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SEVERE CHILDHOOD OBESITY: BEHAVIOURAL AND PHARMACOLOGICAL TREATMENT

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"It looks simple…but it doesn't mean it's easy"

Insoo Kim Berg 1934-2007

ABSTRACT

Background

Childhood obesity is a chronic disease associated with increased morbidity, psychosocial problems and reduced life expectancy, all of which is today very common. Despite this, long-term studies of behavioural treatment of childhood obesity are currently lacking. In addition, behavioural treatment has often only a modest effect and the number of children and adolescents who drop out during treatment is very high. Therefore, additional treatment with antiobesity drugs may be of importance. This thesis evaluates pharmacological and long-term behavioural treatment of severely obese patients in a hospital setting. It includes the first studies published evaluating the effect of three years of behavioural treatment, as well as one study in which the effect of the lipid intestinal uptake inhibitor orlistat is studied in prepubertal children. Finally, the effect of sibutramine, a drug that increases satiety, is studied in severely obese children with hypothalamic obesity and children with obesity in combination with aggravating syndromes.

Aims

The primary aims for the *behavioural treatment studies* were to investigate whether age when treatment is initiated had an effect on treatment outcome and whether the degree of obesity predicts treatment efficacy. The secondary aims were to study whether gender, socio-economic factors, parental weight or age at obesity onset had any effect on outcome and, furthermore, to evaluate factors associated with risk for drop-out. In the *pharmacological studies* the aim was to study orlistat treatment of prepubertal children with regard to tolerance, safety and psychological well-being. The aim of the Sibutramine Study was to investigate whether the drug is effective for obese children who have other diseases that make behavioural treatment ineffective.

Material and Methods

All children were treated from 1998 to 2007 at the National Childhood Obesity Centre, Karolinska University Hospital, Huddinge. Papers I and II include, in total, 643 patients, 6–16 years of age, with simple obesity treated with behavioural treatment therapy for three years. The children were divided into three age groups based on their age at the start of treatment, 6–9, 10–13 and 14–16. In Paper II the subjects were further assigned to two groups: moderate obesity, < 3.5 BMI SDS, or severe obesity, > 3.5 BMI SDS. In the Orlistat Study, Paper III, 11 severely obese prepubertal children (age 8.3–12.3 yrs), BMI SDS 5.3–9.2) were recruited for a 12-week open treatment. The children received the standard adult dose, i.e. 120 mg three to four times daily. Before, during and at the end of the study period the participants were investigated with psychological evaluation, blood chemistry and parameters reflecting obesity and fat mass. The Sibutramine Study was a double-blind, placebo-controlled, cross -over study. 50 children (7–20 years of age) with hypothalamic obesity or obesity with aggravating syndromes were randomised in diagnostic pairs. The initial sibutramine/placebo dose was 10 mg. The treatment period was 20 + 20 weeks, followed by a 6-month open phase. The primary efficacy variable was change in BMI SDS.

Results

In the behavioural treatment studies, the decline in mean BMI SDS was most pronounced in the youngest age group ($P = 0.001$). Pronounced treatment effects were found in moderately and severely obese children in the younger age groups. No effect was observed in severely obese adolescents. Only a weak correlation was found between treatment effect during the first year and BMI SDS change from the start to the end of year three, $r = 0.51$ ($P < 0.001$). Only 30% in the oldest age group remained in treatment for three years. The participants were able to comply with the treatment with orlistat and expressed a desire to continue the treatment after the study period. The side effects were mild and tolerable. No negative effects on psychological or physical well-being were detected. In the Sibutramine Study there was a clinically and statistically significant difference ($P < 0.001$) between the active drug and placebo. The response of children with hypothalamic obesity ($P = 0.005$) was significant but less pronounced than that of children with non-hypothalamic obesity ($P = 0.001$). A continued reduction was observed during the open phase. The treatment was well tolerated by all children.

Conclusions

Behavioural treatment is successful when initiated at 6–9 years of life in both moderately and severely obese children. Age was the only dependent factor for treatment success and predictor for drop-out. Adolescents with severe obesity need special attention. Obese prepubertal children who used orlistat were able to reduce their fat intake and it is possible that orlistat could be used in motivated prepubertal children. Sibutramine might be a suitable aid for children with hypothalamic obesity and aggravating syndromes if sibutramine was approved by EMEA for this age group.

LIST OF PUBLICATIONS

I. **Danielsson P**, Svensson V, Kowalski J, Nyberg G, Ekblom Ö and Marcus C.
Importance of age for three-year continuous behavioral obesity treatment success and dropout rate.
Obesity Facts, accepted for publication Oct 2011.

II. **Danielsson P**, Kowlaski J, Ekblom Ö and Marcus C.
Severely obese children but not severely obese adolescents respond to behavioral treatment.
Submitted

III. Norgren S, **Danielsson P**, Jurold R, Lötborn M and Marcus C.
Orlistat treatment in obese prepubertal children: a pilot study.
Acta Paediatrica 2003; 92: 666-670.

IV. **Danielsson P**, Janson A, Norgren S and Marcus C.
Impact Sibutramine Therapy in Children with Hypothalamic Obesity or Obesity with Aggravting Syndromes.
The Journal of Clinical Endocrinology and Metabolism 2007; 92(11):4101-4106.

CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention Deficiency Hyperactivity Disorder
AD-36	Human Adenovirus-36
ALAT	Alanine aminotransferase
ALP	Alkaline Phosphatase
ASD	Autism Spectrum Disorder
BMI	Body Mass Index
BMI SDS	Body Mass Index Standard Deviation Score
BVCF	Baseline Value Carried Forward
ChEAT	Children's Eating Attitudes Test
CBT	Cognitive Behavioral therapy
CVD	Cardio Vascular Disease
DEXA	Dual-energy x-ray absorptiometry
FAS	Full Analysis Population
FTO	Fat mass and obesity related
Gamma-GT	Glutamyltransferase
GI	Glycemic Index
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
ITT	Intention To Treat
LCHF	Low Carbohydrate High Fat
LMBB	Laurence Moon Bardet Biedle
LOCF	Last Observation Carried Forward
MC4R	Melancortin-4 Receptor
MI	Motivational Interviewing
MMC	Myelomeningocele
MR	Mental Retardation
OC	Observed Cases
PCOS	Polycystic Ovarie Syndrome
PWS	Prader Willi Syndrome
RCT	Randomized Control Study
SCB	Statistics Sweden
SDS	Standard Deviation Score
SEI	Swedish socioeconomic categories
SES	Socio Economic Status
SSRI	Selective Serotonin Reuptake Inhibitor
SSYK	Swedish Standard Classification of Occupations
STOPP	Stockholm Obesity Prevention Program
TSH	Thyroid-stimulating hormone
T3	Tridothyronine
T4	Thyroxine
VAS	Visual Analogue Scale
VLCD	Very Low Calorie Diet

1 PERSONAL NOTES

Today we are aware of the fact that the prevalence of overweight and obesity among children and adolescents has reached epidemic proportions worldwide. In the population of Swedish 10-year-olds, 15–20% are overweight and 3–5% are obese. Again, today we know that obese children's risk of becoming obese adults is alarming. The medical risks and health consequences are both high and dramatic. Childhood obesity increases the same risk for obesity-related diseases as for adults.

In 1997 we thought that severe obesity was a rare condition. When I, together with my supervisor, Claude Marcus, founded the National Childhood Obesity Centre we aimed to create a treatment for a small number of patients, but we were wrong. We soon realised that the number of severely obese children and adolescents was huge. When we invited paediatricians to refer severely obese children it was it was like starting a tidal wave. But what should we do to help all this children? The most common form of treatment then, as well as today, was behavioural treatment, with a focus on eating habits and reducing a sedentary lifestyle. This works for some, but not for all.

I read a lot, attended conferences and listened to experts with a lot of experience. They told me what to do, but the results supporting the recommendations were poor. There were a lot of studies, but generally the studies had too small samples, had short intervention times and were without control groups. Cochrane and the Swedish SBU have conducted large reviews, but they could not find any trials with more than two years of treatment time. And this is strange, considering that obesity is a lifelong disease requiring lifelong treatment.

One year later in 1998 the first antiobesity drug was on the market, Xenical®. Many families felt sure now that the problem was solved. However, Xenical® was not evaluated for children and adolescents. It can be questioned whether it is possible and ethically right to treat growing children with an antiobesity drug. In the summer of 1999 we initiated my first study to evaluate whether it is possible for prepubertal children to use Xenical®.

In 1999 it was time for the next antiobesity drug, Reductil®. This drug reduces appetite but, to do that, it works in the central nervous system. It must be better, however, to lose weight without the diarrhoea associated with Xenical® therapy. Quite soon we started to think about the possibility of helping the subgroup of obese children with morbid obesity and a very low quality of life with this drug. These are children suffering from hypothalamic obesity and children with obesity in combination with aggravating syndromes. These groups of children cannot adapt at all to the behavioural modification therapies.

In 2002 I became a PhD student at Karolinska Institutet and one year later we started to include patients with special needs in the Reductil®/sibutramine study.

In order to be able to evaluate different treatment forms and follow all obese children during treatment in Sweden, in 2005 we initiated the National Health Care Register for Childhood Obesity, BORIS, supervised by the Swedish Association of Local Authorities and Regions and the National Board of Health and Welfare.

In 2008 we had a sufficient number of patients to do a follow-up of three years of behavioural treatment at the National Childhood Obesity Centre, and this may be the reason for the lack of a long-term study and the lack of control groups. The treatment of childhood obesity is still quit a new discipline, so it is difficult to have results for so long time and we cannot stand so many children without treatment for such a long time just because we want them as a control group.

The purpose of my PhD studies is to study some clinically important aspects of childhood obesity treatment, which may ultimately and at least to some extend improve the treatment and care for children suffering from obesity.

2 INTRODUCTION

2.1 CHILDHOOD OVERWEIGHT AND OBESITY

Today all are well aware of the fact that overweight and obesity in children is a huge and overwhelming problem worldwide. Children of today are at risk of becoming the first generation that dies at an earlier age than their parents[1]. The understanding of the causes and consequences of childhood obesity has greatly increased during recent years. However, the management of this patient group remains unclear. It seems that all experts agree that step one is prevention. However, some children will become obese regardless of prevention. In other words, a universal prevention programme cannot replace the need for an organised obesity treatment.

2.1.1 Definition of childhood overweight and obesity

Overweight is a state at risk of developing the disease obesity. Today the cut-offs for overweight and obesity differs between countries and research groups. In the adult population the standard classification of obesity is based on the body mass index (BMI). BMI is calculated as weight in kilograms divided by height in metres squared (weight/height^2). Adults are classified and defined by the World Health Organisation as overweight if BMI is ≥25 and obese if BMI is >30[2]. These definitions are height-dependent. Furthermore, BMI does not discriminate as to whether the increased weight is due to increased muscle mass or fat. These definitions cannot be used for children since BMI changes considerably with age, height and also, to a minor extent, with gender. The most used international definition of childhood obesity is the one adopted by International Obesity Task Force (IOTF) based on Cole's age and gender-specific cut-off points corresponding to the adult criteria of a BMI of 25 for overweight and 30 for obesity[3].

To be able to compare weight data between children of different ages and gender and to analyse differences over time, a BMI standardised age- and gender-dependent deviation score (SDS) is used. In Sweden we usually use two different reference populations, the first determined by Rolland-Cachera based on a French population during 1953-1969[4] and the second by Karlberg based on Swedish children[5].

2.1.2 Causes of childhood obesity

Childhood obesity – as well as obesity in general - is always the result of an imbalance between energy intake and energy expenditure. Many factors may affect the risk of coming into an imbalanced state, such as genetic/epigenetic vulnerability and many other ones, some of which are discussed below.

Eating habits. There is much discussion about children eating more 'fast foods', larger portion sizes, foods with higher fat and sugar content, less fruits and vegetables, more sweets, soft drinks and snacks. We celebrate, comfort and eat more often than our parents did and that this would be one of the major culprits for today's obesity epidemic. Nevertheless, there is modest evidence that overweight and obese children eat more and in a different way than normal-weight children[6, 7]. The only positive association with intake and obesity is in the consumption of sugar-sweetened beverages. A prospective study in

children aged 11–12 years found that this consumption was associated with a 60% increased risk of obesity[8]. It may be that the dietary causes are poorly understood, probably due to difficulties in making accurate assessments of diet in children[9].

Physical activity decreases, television viewing and other sedentary behaviours increase. The technological options for enjoyable sedentary behaviours are increasing. To watch television has been directly linked to obesity in childhood, with a rate of obesity that is 8.3 times greater among children who watched more than 5 h of television per day compared with those who watch up to 2 h per day[10]. Researchers suggest that obese children are slightly less physically active; however, energy expenditure due to physical activity does not seem to differ[11-14]. These findings are attenuated to some extent due to methodological limitations.

Heredity, i.e. parental obesity, has been identified as a major risk factor for childhood obesity, probably due to a combination of genetic, epigenetic, social and environmental factors[15, 16]. Social factors seem to be of some importance for BMI heritability since associations have been found between the BMI of adoptees and adoptive parents. However, these associations are much stronger between the child and its biological parents[17]. Children with two obese parents have a higher risk of obesity than those with one or no obese parent[16]. The impact of parental BMI on the severity of obesity in children is strengthened as the child grows into adolescence[18].

Genetic factors have been suggested to affect behavioral factors by altering satiety, appetite or physical activity patterns, but may also alter substrate utilisation. Genome-wide association studies have identified several common genetic variants associated with high adiposity and obesity, but each with weak effects. The first of common mutations found were in the melanocortin-4-receptor (MC4R), affecting less than 5% of obese children[19]. The most important one found so far is the fat mass and obesity-associated gene, FTO. This is a common gene variant in the population that increases the risk of overweight and obesity. It was discovered in England when screening for susceptibility genes for typ 2 diabetes. Sixteen per cent of the European population which had inherited the gene variant in duplicate, homozygote, have a 67% increased risk of obesity compared with those without the variant. For a single set the risk is 38% and the average difference for those with and without the risk gene is 3 kg[20]. A study conducted by Jacobsson et al. suggests that FTO may have an important role for gender-specific development of severe obesity and insulin resistance in children[21]. Interestingly, it has been shown that physical activity takes away the effect of the gene[22].

Current research appears to continuously widen the horizon of possible factors of importance for the obesity epidemic seen today. I have chosen to describe some of these. However, it is important to look critically at these factors because it is often difficult to rule out what is the cause and what is the effect?

Sleep. Some studies have shown that fewer hours of sleep are associated with an increased BMI both in children and adults[23, 24]. Children 5–10 years old with the least amount of sleep, 8–10 hours per night, had a 3.45–4.9 times higher risk of being classified overweight

than children sleeping longer[23, 25, 26]. Spruyt et al. studied how sleep duration and regularity affect body weight[27]. He found conflicting results, the average sleeping time for children aged 4–10, regardless of degree of obesity, was only 8 hours a night. The obese children experienced more variable total sleep times on weekends than on schooldays, with shorter sleep duration on weekends. This is to be compared with normal-weighted and overweight children who have maintained relatively steady sleep patterns throughout the week, although normal-weighted children generally slept longer or got "catch-up sleep" on weekends[27]. A number of possible explanations for how sleep deprivation might affect food intake have been proposed. Decreased leptin and increased ghrelin levels are associated with sleep deprivation and both hormone changes may induce increased food intake[24]. Other studies indicate and speculate that poor sleep can affect the body's biological clocks. The diurnal rythmicity of cortisol and insulin, two hormones, which, when out of balance, are closely associated with weight gain, heart disease and diabetes, are affected by sleep deficits24.

Viruses. Some investigators are skeptical about the claim that the dramatic change in the prevalence of obesity can only be due to changes in dietary intake and physical activity. In several animal models researchers have found that viruses have been shown to cause obesity In US adults. Atkins et al. found that 30% were infected with human adenovirus-36 (Ad-36) and had 9 units higher BMI compared with those not infected[28]. The same pattern was seen in obese Korean children with 30% positive and significantly higher BMI and waist circumferences[29]. Thus, Ad-36 may have a function in the obesity epidemic.

Epigenetics. Environmental factors may affect DNA activity without changing the DNA molecule itself. Small molecules can bind to the DNA strain and thereby reduce the activity of specific genes. These genetic modifications may be hereditary. Thus, environmental factors *in utero* can have long-term effects and even affect the next generation[30]. One example of this is the study conducted by Kral et al. in which he observed that mothers who have undergone bariatric surgery give birth to leaner children after than before the surgery[31]. However, the relevance of imprinted genes to our understanding of obesity in the general population is still uncertain.

"*Epigenetics has always been all the weird and wonderful things that can't be explained by genetics.*"
Denise Barlow (Vienna, Austria)

The majority of obese children have no underlying medical disorder that causes their obesity. However, there are syndromes in which severe obesity is a dominant feature. Furthermore, children who suffer hypothalamic damage as a consequence of tumours and subsequent surgery in the central nervous system develop severe obesity in up to 50% of cases.

2.1.2.1 Prader Willi Syndrome

PWS is an autosomal dominant disorder and the most common obesity syndrome, occurring at a rate of approximately 1/25,000 live births[32], in Sweden 10–12 birth each year, and affects both boys and girls. The syndrome is caused by a small deletion of the long arm in chromosome 15 when the deletion comes from the father. When the deletion comes from the maternal genome, another syndrome occurs.

Specific characteristics: *Neurological* comprises hypotonia and hypothalamic dysfunctions. The hypotonia occurs as early as during the neonatal period and results in decreased movement, weak crys and poor sucking. The poor sucking leads to feeding difficulties. Hypothalamic dysfunctions are manifested in decreased salivation, increased tolerance to pain and altered sleep control leading to daytime sleepiness when the children become older. *Craniofacial and ophthalmological abnormalities.* PWS children are characterised by a facial feature with thin upper lip and a down-turned triangular-shaped mouth. They have almond-shaped eyes. A relative hypopigmentation of the hair, eyes and skin is common. There are dental anomalies and decreased saliva flow with viscous and sticky saliva. *Growth and stature.* Birth weight and length are usually within normal limits. Thereafter, due to a deficiency of growth hormone and the lack of the pubertal growth spurt, the children almost always have a short stature. If not treated with growth hormone, the average adult height is 155 cm for males and 148 cm for females. The hands are small and narrow and the feet short and broad. *Musculoskeletal:* scoliosis or kyphosis, or both, are common. Osteoporosis also occurs frequently. *Hyperphagia and obesity.* In early childhood, between 1 and 6 years of age, hyperphagia and obesity begin. Hyperphagia is thought to be due a hypothalamic abnormality causing a lack of satiety. The lack of satiety leads to food-seeking behaviour and an abnormal eating pattern with slow but continuous eating compared with the deceleration eating pattern observed in obese and normal-weight children[33]. These abnormalities, together with a low metabolic rate, contribute to obesity. Due to a growth hormone deficiency, lean body mass is decreased, which results in a high ratio of fat to lean body mass. *Endocrine.* Hypogonadism is manifested as genital hypoplasia. Diabetes type II is more common in individuals with PWS probably due to the obesity in combination with reduced physical activity. *Developmental delay and mental retardation.* Most individuals with PWS are in the mild mental retardation range and have multiple learning disabilities. *Behavioural.* The children suffering from PWS shows a large spectrum of behavioural problems. The problems occur at about 4 years of age and seem to be strongly related to the insatiable appetite and carvings for food. This behavioural problem includes rages, stubbornness and controlling and manipulative behaviour. To get food, it is also usual to lie and steal. The problems with overeating and obesity lead to a poor self-image and feelings of being out of control and isolated. All these problems may predispose to depression and anxiety.

Management: The most important things for these children and families are as early a diagnosis as possible in order to initiate set procedures and supplementary treatment with growth hormones. These children are in great need of strict routines; changes should be carefully planned. An early and consistent diet routine with fixed measuring procedures and special diets and support for parents in setting boundaries and coming in contact with other affected families.

2.1.2.2 Laurence Moon Bardet Biedle (LMBB)

This is a rare autosomal recessive disorder with a mutation in 6 identified loci so far. It is still a quite unknown syndrome and is not always correctly diagnosed. The prevalence in Europe is 1:150,000–160,000. In Sweden 1–4 children are born with it each year (= 1: 25–100,000). The most dominant features include retinitis pigmentosa leading to blindness, postaxial polydactyly, central obesity, learning disability, hypogonadism in males and renal dysfunction. This is a disease with an adverse prognosis and the children are in urgent need of an early diagnose and special care to reduce stigmatisation.
There is no definite treatment, but symptomatic, supportive and rehabilitative measures can reduce the disability. These include dietary modification, oral hypoglycaemic drugs, testosterone supplement etc.[34].

2.1.2.3 Hypothalamic damage, and central nervous system disturbances

Brain tumours
Craniopharyngioamas are slow growing benign brain tumours. They occur mostly in children and young adults. Males and females are affected equally. The first signs include poor growth in children, often in combination with weight gain. An increased awareness of these symptoms should result in earlier detection of the tumours. Later, symptoms of intracranial pressure such as headache, vomiting and imbalance, visual changes, increased thirst and urination, are dominant. It is classified as benign, but the treatment is difficult and significant morbidities are associated with both the tumour and treatment. Obesity is a major concern in children treated for craniopharyngioma and is caused by hypothalamic damage after restriction, but also the damage caused by the tumour itself before detection is of importance. The prevalence of obesity has been evaluated to be 50% of patients, one third of which are morbidly obese[35].

Intellectual disability
Adolescents with intellectual disability are a group of individuals at higher risk of developing obesity and related morbidities. It has been shown that they have a higher percentage of total fat mass, wider waist circumferences, lower levels of fat-free mass, lower bone mineral density, higher insulin and poorer cardiovascular fitness. Altogether, they have a significantly higher prevalence of cardiometabolic risk factors compared with those without an intellectual disability[36].

Down's syndrome
Down's syndrome is a genetic condition that causes delays in physical and intellectual development. It has been suggested that the higher frequency of overweight in this group could be dependent on a lower basal metabolic rate. The children with Down's syndrome should be handled separately from other children with an intellectual disability since they differ in body constitution, especially short height, a tendency towards thyroid dysfunction (hypothyroidism) and congenital heart defects. Compared with other children with an intellectual disability, Down's syndrome is associated with a higher cardiometabolic risk and a lower systolic blood pressure[36].

Attention deficit/hyperactivity disorder, ADHD

The potential relationship between obesity and ADHD has not been sufficiently studied. Raising awareness of the relationship between these two conditions is of great clinical importance. It has been shown that the combination is more common than we previously thought, this probably being due to the fact that the obesity masks the hyperactivity because the obese individuals are less mobile[37]. A study conducted in 38 patients at the National Childhood Obesity Centre showed that more than one half of the group had indications of problems within a spectrum of attention deficits. None of the children had a clinically verified diagnose before the study[38].

2.1.3 Prevalence of childhood obesity

Childhood obesity is a worldwide problem that has reached epidemic proportions. The European IDEFICS study shows a prevalence of 8–11% overweight and 4–6% obese among 4–5-year-olds, corresponding values for 9–11-year-olds being 19–20% overweight and 6–8% obese[39]. Among Swedish children, the current prevalence of overweight amounts to 15–20%, and 3–5% are obese[40, 41].

Recent statistics suggest that the prevalence of childhood obesity might be stabilising in several developed countries[42-44]. In Sweden the prevalence seems to have levelled off at around 17% overweight and 3% obesity among 7–9 year-olds[45] and between 2.4–4.7% obesity and 15.9–24.1 overweight among 10–11 year-olds[46]. Also among 4-year-olds the situation seems to have stabilised, but the regional and socioeconomic differences are pronounced[47].

This levelling off may have a number of possible explanations:

- All efforts to prevent and treat may have had a collective effect.
- All publicity may have helped to raise public awareness of the severity.
- Better and informative food labelling might have helped the consumer to make better choices[48].

In Sweden there are regional differences in the prevalence between children living in cities and those living in rural areas[45, 46, 49, 50], as well as pronounced socioeconomic and regional differences[45]. Thus, despite the fact that, at least at the moment, the prevalence is not increasing, we have a huge problem in Sweden. We have never had so many obese children and adolescents. Furthermore, the increasing socioeconomic gradient is a concern in itself.

2.1.4 Health consequences of childhood obesity

There is a complex chain of metabolic disorders associated with obesity that develops over a long period. Because of the silent progress and unclear guidelines about reference values and tests, especially among children, co-morbidities in obese patients have been left undiagnosed, which makes the prevalence uncertain.

Obesity persistence

Obesity in childhood is not simply a matter of being too fat. The medical risks and health consequences for obese patients are dramatic. Obesity increases the risk for cardiovascular and endocrine disorders, the metabolic syndrome, different cancers, psychological problems and social consequences. These co-morbidities significantly increase mortality and reduce the quality of life[51]. Overweight in childhood increases the risk (OR = 6.2) of remaining overweight as adults[52]. A study on Slovenian adolescents (n = 4833, 18-year-olds) found that 40% of obese males and 49% of obese females were obese as seven-year-olds[53].

Insulin resistance

An early consequence of obesity is disturbed glucose and insulin homeostasis[54]. It has been shown that obesity in children is associated with decreased insulin sensitivity and increased circulating insulin and that these abnormalities persist into young adulthood[55]. Insulin resistance is an important factor in the development of type 2 diabetes. All obese children from 6 years of age treated at the National Childhood Obesity Centre appeared to develop insulin resistance of some degree[54], but there are marked individual differences. We could only explain 26% of insulin sensitivity variability by age, gender, adiposity and physical fitness; however, within this group of severely obese subjects, the degree of obesity (BMI or fat percentage) is of limited importance[54]. Thus, the mechanisms behind insulin resistance are still unclear. Most probably both environmental and genetic factors are involved. Except for the risk of progression to type 2 diabetes, a disturbed insulin and glucose metabolism may contribute to other metabolic consequences such as high blood pressure and cholesterol levels[1]. Clinical features: One of the first signs of insulin resistance is acanthosis nigricance, a brown to black hyperpigmention of the skin, especially in the neck, waist and axilla.

Two prediabetic states have been defined: impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). These are risk factors for developing future type 2 diabetes[56]. Obesity increases the risk for IFG. IFG is defined differently by the World Health Organisation and the American Diabetes Associations (f-glucose ≥ 5.6 mmol/l and ≥ 6.1 mmol/l, respectively). Except for the risk of future diabetes, IFG is also correlated with other future morbidities in adults, such as cardiovascular events and cancer[57, 58]. The prevalence of IFG is high among Swedish children and adolescents (17%). Also prepubertal children have a high prevalence of around 11% (www.e-boris.se).

Another prediabetic state is IGT. This is a measurement of reduced glucose elimination that has not yet reached the type 2 diabetes level. This is diagnosed with an oral glucose tolerance test (OGTT). OGTT is not as frequently performed as fasting glucose samples and therefore it is not that easy to define the prevalence of IGT. Out of the severely obese children at the National Childhood Obesity Centre, 20% had IGT (> 7.8 mmol/l) (www.e-boris.se).

Chronic inflammation

A shared cause of many of the metabolic comorbidities, such as insulin resistance and hypertension, might be a low grade of systemic inflammation. This inflammation is associated with increasing adipose tissue, resulting in higher levels of proinflammatory cytokines. A primary source for many of these cytokines is the immune cells located in the expanded adipose tissue[59] . The association between obesity and systemic inflammation is well recognised in adults. Data for youths are also emerging. Visser et al. found that overweight children aged 8–16 were, independently of other risk factors, associated with increased serum C reactive protein concentration[60].

Hyperlipidemia

Dyslipidemia may occur in children and adolescents as a result of obesity. The most common abnormality of lipids and lipoproteins associated with obesity is an increase in triglycerides and a decrease in high-density lipoprotein cholesterol. Dyslipidemia has potential to accelerate atherosclerosis and is an important part of the metabolic syndrome[51].

Fatty liver disease

Fatty liver disease is often termed more correctly as non-alcoholic fatty liver disease (NAFLD). It is a typically silent disease detected as an asymptomatic elevation of the hepatic transaminases. The severity of the disease differs widely, from accumulation of fat in the liver alone (steatosis) to fatty infiltration with inflammation (steatohepatitis), which leads to the potential progression to cirrhosis. The estimated prevalence of NAFLD differs between countries, but reports indicate that 23–53% of obese children are afflicted. In normal-weighted children the prevalence is estimated to be 3%[61].

Blood pressure disturbances

A consistent positive association between body size and blood pressure level has been observed throughout childhood. However, blood pressure rarely reaches levels that require pharmacological treatment.

Another problem associated with obesity is the disturbed diurnal variation. Ambulatory blood pressure monitoring provides an opportunity to study blood pressure (BP) patterns over day and night. In adolescents, nighttime (sleep) systolic blood pressure normally drops by ~10% from daytime (awake) blood pressure, i.e. the phenomenon of nocturnal dipping. Our group has observed that obese adolescents are at higher risk of blunted nocturnal blood pressure dipping (< 10%) and may therefore be at increased risk of blood pressure-related complications[62].

Metabolic syndrome

The metabolic syndrome may be characterised by the clustering of three or more of the following risk factors: hypertension, hyperglycemia, elevated levels of triglycerides (TGs), low levels of high-density lipoprotein (HDL-C) and adiposity. The prevalence of the metabolic syndrome has increased worldwide, parallel to the rising rates of overweight and obesity, and clustering of metabolic risk factors has been observed in children and adolescents[63]. Obesity increases the risk for the metabolic syndrome[64], which in turn is a risk factor for several diseases and premature death[65]. The reported prevalence of the

metabolic syndrome in children varies and can be as high as 50% in obese adolescents[64]. It appears that children with the metabolic syndrome have a threefold higher prevalence of the syndrome in adulthood. The definition of the metabolic syndrome varies across countries. In Sweden, the definition by the International Diabetes Federation is generally used and requires central obesity plus two of the following four: elevated triglycerides, reduced high-density-lipoprotein (HDL) cholesterol, hypertension and impaired glucose tolerance or type II diabetes.

Type 2 diabetes

Type 2 diabetes is a consequence of the combination of insulin resistance and an inability of beta-cells in the pancreas to secrete sufficient amounts of insulin to maintain normoglycaemia. The development of type 2 diabetes is infrequent before the age of ten. It is more frequent in girls and varies greatly with ethnicity[66, 67]. In Sweden the number of children with type 2 diabetes is still low despite the high prevalence of children and adolescents with obesity. To date, only 65 adolescents have the diagnosis of type 2 diabetes in the Swedish Childhood Diabetes Register (Swediabkids). However, silent diabetes may go undiagnosed during many years. Untreated, type 2 diabetes may ultimately lead to several secondary outcomes such as nephropathy and micro- and macroangiopathies.

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is defined by irregular or absent menstruation, hyperandrogenism and polycystic ovaries. The visible symptoms of this condition cause the affected girls a lot of distress; they have hirsutism, together with severe acne and acantosis nigricans. Furthermore, the polycystic ovaries lead to ovulation becoming less frequent or absent and complicate pregnancy.

Gynecomastia

For the obese boys, the problem which is usually most embarrassing in addition to obesity itself is the breast gland enlargement due to the fact that aromatases in adipose tissue convert testosterone to estrogens. Furthermore, it appears that obese boys are affected by micropenis. It is unclear whether there is a true poor penile growth associated with obesity or whether the explanation is that the enlarged layer of fat in the pubic area hides most of the penis.

Sleep apnea

Sleep apnoea leads to disrupted sleep and daytime sleepiness. This could be a problem for children to stay awake and perform during school-time. Sleep apnea might result in low oxygenation. This in turn affects blood pressure and might also cause cardiomegaly and increase the risk of cardiac infarction[1].

Cardiovascular disease

Childhood obesity has been shown in several studies to be associated with an increased risk for cardiovascular disease in adulthood[1, 68]. Cardiovascular disease (CVD) and risk factors associated with obesity are high blood pressure (hypertension), increased thickness of the main pumping chamber (left ventricular hypertrophy), increased hardening of the arteries (atherosclerosis), high cholesterol and dyslipidemia. These changes have been seen in different degrees in children with obesity depending on the degree of obesity and age[69-72].

Orthopedic problems

Obese individuals often have pain in their joints. To some extent, this is due to the increased weight load on the joints, bones and muscles in combination with low vitamin D levels and an abnormal load secondary to the incorrect stature induced by obesity. In addition, there are certain conditions that need to be excluded: *Blount's disease* is a rare diagnosis with abnormal growth in the tibial epiphysis which leads to a more angulated knee. Among those affected, overweight and obese individuals are over-represented. *Slipped upper femoral epiphysis (SUFE)* occurs as an effect of increased weight on the growth plate of the hip and leads to pain in the hip and/or knee and limping. For both this conditions, sustained weight reduction is necessary. The obesity-caused orthopaedic complications can be detected early in life. As early as from the age of four years the obese children already have a lower arch and are more flat-footed[73]. Obese eight-year-olds can already display increased plantar pressure at rest and during movement, can be expected to cause orthopedic problems later in life[74].

Psychosocial problems

Probably the most onerous burden for the obese children is the psychological and social consequences. As early as 1967 a research group in the U.S. showed how young boys 6–10 years of age described in negative words person with a fat body as one who cheats and is lazy, sloppy, naughty, mean, ugly, dirty and stupid[75]. Since the prevalence of obesity has increased, one could hope that an acceptance of the condition would also increase. In 2001 Latner et al. replicated the study from 1961. The children aged 10–11 years ranked six drawings of children with various handicaps (crutches, wheelchair, missing a hand, facial disfigurement, obese and healthy): the one they would like to play with first etc. Unfortunately, they obtained the same result as in 1961. The healthy child received the highest score and the obese the lowest. Indeed, the discrepancy had increased so that instead of increased acceptance, they found that the stigmatisation of obesity by children has increased over the last 40 years[76]. Bullying, taunts and ostracism in daily life may contribute to the fact that obese children are overrepresented with depression[77] and a low quality of life[78, 79]. It is not just society's view of the individual that makes it difficult, sometimes even the professionals have problems with seeing these patients in a respectful manner. This is a conclusion from an article about patients undergoing surgery for craniopharyngioma.

> *"Whatsoever, the worst complication of craniophayngioma is blindness; all our efforts to prevent it from happening are warranted and endocrine complications may be the price for the patient to pay. Looking at an obese self in the mirror is terrible but certainly better than not being able to see oneself in a mirror at all" (Vinchon Childs Nerv Syst 2009 s. 351)[35].*

For obese children, this chronic disease requires a respectful lifetime treatment.

2.2 TREATMENT OF CHILDHOOD OBESITY

General aspects on behavioural treatment

The most common form, the cornerstone and first line of treatment for overweight and obesity, is behaviourally based interventions. These interventions promote weight loss through modifications in the diet and activity level and involve entire families.

Treatment of obesity is always difficult, but to treat obese children may even be more problematic than to treat adults. The adult patient has a personal responsibility and the risks of secondary diseases are present.

How do we get the children to understand that they must make sacrifices in their daily life now to avoid diseases as adults? And, how do we get the often busy parents to cope with the treatment? Many times the patient and the family are unaware of the problem of obesity[80]. Therefore, the first step is to get the families to understand the severity of the disease and admit the need for help. For the very young child, information should be given to the parents with the child's attendance. On the other hand, when treating adolescents, it is important to respect the process of independence and discuss health behaviours directly with the patient but with the parents' attendance[81]. The treatment of obesity should be started in children with obesity from the age of six years and at the same age children with overweight need to be identified. For children younger than four year of age, general advice about a healthy lifestyle should be given to all families.

Treatment should not be primarily guided by the child's motivation, but mostly by the severity of the disease. To estimate the severity of the obesity, we must examine the child and check blood samples since the majority of the complications are asymptomatic.

All treatments must be long-term and should, when possible, be conducted by a special multi-disciplinary team with the support of and in close cooperation with school health services and primary care. Most often the treatment requires frequent visits to increase the likelihood that the child and parents should understand how changes in eating and activity habits yield results for body mass improvements. It is important that children with obesity who have undergone treatment with successful results continue to be followed. Obesity is a lifelong disease requiring lifelong treatment.

2.2.1 Behavioural treatment

The goal of behavioural treatment is to achieve a long-standing weight loss and thereafter weight maintenance. This should be done through:

- Reduced energy intake
- Increased energy expenditure
- Decreased sedentary activities

To accomplish this, parents are engaged and other caregivers are involved in the child's daily life. It is generally recommended that all these changes are best adapted in small steps with realistic milestones. The intensity and technique are determined by the age of the patient, the degree of obesity, individual health risks, psychobehavioural characteristics, morbidity and outcome of previous weight-loss attempts.

2.2.1.1 Diet

The overall objective of dietary management is to induce weight loss by means of reduced energy intake. The aim is also to establish good eating habits. This means regular meals, increased intake of fruit and vegetables, reducing portion sizes, the right choice of beverage and restrictions on junk food and snacking. One specific aspect that seems to be of importance is fluid intake and drinking habits. Consumptions of soft drinks induces to a lesser extent satiety[82]. Sugar in liquid form is fraudulent because these calories are added to the other solid food instead of replacing parts of it[8].

We must take into account the child's age and degree of obesity. The best and simplest method is to assess the patient's current intake, meal patterns and family circumstances and make changes accordingly. All changes should be agreed with the family and following the rule of a few changes at a time, the 'small-step' approach. Recommended food follows the recommendations of the Swedish National Food Administration (www.slv.se).
The most important thing about dietary advice to children is that it should be as simple as possible so the child can live as normal a life as possible. Children need learn strategies to be able to eat school meals, meals with friends and to go to a party.

It has to be pointed out that most of the above-mentioned recommendations are based on common sense and experience and are not evidence-based[80, 81, 83, 84].
The new, often discussed diets with low or high fat and carbohydrates and a reduced glycaemic load diet (GI) have not been evaluated and therefore are not recommended for children.

2.2.1.2 Physical activity

Sweden follows the Nordic recommendations of at least 60 minutes of physical activity per day. This activity can be divided into several sessions and should be at least of moderate intensity level. There are indications, however, that there is a need for a longer time to optimise the health-promoting effects of physical activity[85]. It is also possible that there is a need for both a moderate and high-intensity level to achieve the effect on BMI[86]. But how much physical activity can the obese child handle and manage? This is difficult to answer and very individual; all obese children are not inactive, although many are, but therefore we should not generalise. Ekelund et al. found that obese adolescents are less physically active than normal-weighted ones, but the physical activity-related energy expenditure did not differ significantly between the groups[13]. The most plausible explanation could be the increased energy cost of moving a larger body. It is also of importance to emphasise the additional benefits of increased physical activity: for example, reduced cardiovascular risk factors, improvements in body composition and cardio respiratory fitness[87] and perhaps the most important, improved self-esteem[88].

2.2.1.3 Different techniques for inducing behavioural changes

Group interventions can be of many different kinds, such as parent training groups, family therapy groups, weight schools, camps for families or children, physical activity groups with, among things, pool and resistant training.

Various forms of group treatment have been described in which children and parents are separated or gathered. Group therapy appears to be more successful in the younger ages and lower degrees of obesity[89, 90]. In general, group therapy is probably not more effective than individual treatment, but it may be more cost-effective[89]. Therefore, as an initial treatment for young obese subjects, group interventions may be beneficial. But it may be necessary in many cases, and especially in the younger age groups, to reach out to as many patients as possible and it may also be more cost effective. The purpose of the group therapy may be dietary advice, physical activity, help with problem solutions as how to handle festive occasions, and so on.

The *individual visit* provides greater opportunities to tailor treatment to the needs of the particular child and family. The time between visits can be decided based on the particular patient's needs and performance. This means that the individual visit especially suits children and adolescents with special needs.

The Traffic light system developed by Epstein et al.[91] is widely used, probably because of its pedagogical way of dividing food into different categories. It uses three colour-coded categories: red (high calorie density and limited amount of nutrients, such as sweets, snacks, sauces, jam, ice-cream and soft drinks), yellow (for example, meat, fish, dairy products, pasta, rice and bread) and green (low calorie density, for example vegetables and most fruits). Each category has simple written guidelines to determine a number of "credit points" corresponding to a certain amount of the food choice. Each child is allocated a certain number of points from each category according to sex and age[92].

One way to reach especially the non-motivated patient is by so-called *motivational interviewing (MI)*. This is a way of active, reflective listening with shared decision-making and is empathic and respectful so as to enhance the treatment session[93]. This method is widely used, but its effectiveness is not known[48].

Cognitive behavioural therapy (CBT) is a targeted treatment modality characterised by the application of a patient-centred, structured and problem-oriented approach. The treatment is based on an analysis of the patient's problem and modelled around the patient's current needs, resources and difficulties. One could say that CBT is an evidence-based form of psychotherapy in development. Even if you do not work psychotherapeutically with overweight and obesity, it could be beneficial to use some parts of the cognitive principles.

2.2.2 Pharmacological treatment

For many patients behavioural treatment is insufficient and a complement is necessary. Pharmacological agents are potential adjuncts to behavioural interventions for severely obese adolescents[94] but, unfortunately, no pharmacological treatments are available today for children and adolescents in Sweden.

Chiefly drugs with a primary effect on weight should be used for severely obese adolescents, but also for those who do not benefit from behavioural modifications.

Drugs with a direct effect on weight reduction can be divided into:

- Drugs acting in the central nervous system, interfering with neurons involved in appetite and satiety regulation.
- Drugs locally acting in the intestine by inhibiting uptake of nutrients.
- Drugs acting in the central nervous system or peripheral-acting drugs aimed at increasing energy expenditure.

Pharmacological treatment of childhood obesity is controversial and the scientific evidence for these therapies is insufficient. The Cochrane Review from 2009[95] identified ten randomised controlled studies of pharmacological treatment for obese children (60% of these included fewer than 30 participants). In contrast, 54 studies were identified as being based on lifestyle interventions. All the included pharmacological studies were conducted in adolescents.

2.2.2.1 Orlistat

Orlistat or Xenical® acts locally in the gut lumen by inhibiting gastrointestinal lipase. This enzyme normally breaks down triglycerides in the intestine to make them absorbable. Thereby, one reduces the uptake of consumed fat in the diet by 30%. The unabsorbed fat passes through the bowel, resulting in fatty stools. Therefore, the primary side effects if one eats too much fat are steatorrhoea, i.e. oily, loose stools. If this can be understood and handled by the patient, it might induce fat avoidance and thereby weight loss. Orlistat may also interfere with the absorption of fat-soluble vitamins (A, D, E and K). It is therefore recommended that a daily multivitamin supplement should be taken during treatment.

Based on the results of a randomised double-blind placebo-controlled study conducted by Chanoine et al. in the USA in 539 adolescents treated during 12 months, Xenical® has been approved for the treatment of obesity in children from 12 years of age in the USA since 2003. This study showed that BMI had decreased by 0.55 kg/m^2 during orlistat therapy and increased by 0.31 kg/m^2 with placebo[96]. The recommended dose is 120 mg three times daily (together with each meal); this is the same as in adults.

2.2.2.2 Sibutramine

Sibutramine or Reductil® works in the central nervous system by reducing serontonin and noradrenaline reuptake. Sibutramine thereby reduces the appetite and, to some extent, increases energy expenditure. The most common side effects are increased blood pressure and heart rate, dry mouth, insomnia, dizziness and constipation. Regarding long-term outcomes, there has been only one randomised study during 12 months in 498 adolescent patients conducted by Berkowitz et al. in the USA in 2006. After 12 months of treatment the mean change in BMI from baseline in the sibutramine group was -3.1 kg/m^2 versus -0.3 kg/m^2 in the placebo group. Side-effects were tachycardia in 6% and hypertension in 2% of the subjects in the sibutramine group[97].

Since increased cardiovascular events and stroke have been observed during sibutramine treatment in adults in the SCOUT study, it has been withdrawn from the market in major parts of the world.

2.2.2.3 Rimonabant

Rimonabant or Acomplia® is a cannabinoid-1 receptor blocker and is thereby considered to be an appetite suppressant. It works by blocking a cellular receptor in the endocannabinoid system of the brain, which is believed to influence the regulation of body weight, glucose and lipid metabolism. Acomplia® received European Union marketing approval in June 2006, but the drug did not enter the market in the United States. Approval of the drug was officially withdrawn in January 2009 after the statement that the benefits of Acomplia® no longer outweighed its risks due to the possibility of serious psychiatric problems and even suicide.

2.2.2.4 Metformin

Metformin is an old and proven anti-diabetic drug. It is the first-line drug for the treatment of type 2 diabetes and it is not marketed as a weight loss medication. More recently it has been observed that it has a positive effect on weight. Side-effects are few and consist mainly in gastrointestinal distress, especially at the beginning of treatment. A previous review of treatment when lifestyle change is not sufficient by Hearnshaw et al. found a reasonable number of studies involving metformin. The dose varied widely, the studies involved small numbers of patients, short durations and only adolescents with abnormalities in insulin sensitivity. All and all, it is difficult to draw conclusions, but nine of twelve studies in adolescents showed significant reductions in BMI[98].

2.2.2.5 Ephedrine/caffeine

In some countries the combination of caffeine and ephedrine is approved for obesity treatment. There is limited support for this indication in adults[99]. One study in 22 adolescents has been published; it is a 6-month double-blind placebo-controlled trial[100]. The mean decrease in weight in the caffeine-ephedrine group was 6.6 vs 0.5kg in the placebo group. There were no differences in side-effects between the intervention and placebo group.

2.2.3 Very low calorie diet

A very low calorie diet (VLCD) is defined as a protein-sparing diet with only 600-800 kcal per day. VLCD also contains the recommended amounts of nutrients such as vitamins and minerals to be the sole energy and nutrition in the treatment of overweight and obesity. A low calorie diet (LCD) is a similar diet with 900–1200 kcal per day. These highly restrictive diets have not been evaluated in children and only poorly evaluated in adolescents. VLCD causes ketosis, which may reduce appetite. These diets can be tested for morbidly obese adolescents. For some individuals it may be necessary to reach a quick weight loss in order to avoid being affected by disease or before surgery. VLCD is often used during 3 weeks before bariatric surgery to reduce stomach size.

Despite the fact that the products are not drugs, but food consumer products, patients should be closely monitored with blood sampling and frequent visits during the VLCD treatment phase, usually 6–8 weeks. There is a risk of rapid weight gain after VLCD/LCD. Therefore, it is important to introduce food in a careful way after the treatment period.

2.2.4 Surgery

Bariatric surgery (predominantly Roux-en-Y gastric bypass) for the management of severe adult obesity has been shown to be effective in maintaining significant weight loss and improvements in many of the medical complications[101]. There are many ongoing studies for adolescents, but it is still unclear if bariatric surgery is an option for obese adolescents. One randomised controlled study has been published in which the adjustable gastric banding was tested versus behavioural treatment[102]. Although 28% had complications requiring surgery, the two-year results are very promising. In Stockholm we have tested gastric banding with poor results[103] most probably because the study populations differ markedly. Many of our severely obese adolescents have psychosocial problems and find it difficult to comply with the strict regulation and follow-up strategies required when gastric banding is used. Therefore, AMOS was initiated in year 2006. This is a nationwide Swedish ongoing controlled study to assess the safety, efficacy and psychological well-being of gastric bypass in morbidly obese adolescents (age 13–17). At one-year follow-up the results were satisfactory with regard to safety, weight loss and metabolic improvements. The two-year data are still promising[104], but these adolescents require extra follow-up efforts due to psychosocial problems[105].

2.2.5 Goal of treatment

The obvious goal if you treat a disease is to cure it, but in this case the goal should be a weight reduction which results in an iso BMI of < 30. However, this is difficult to achieve and therefore this outcome parameter is rarely used when obesity treatment is evaluated. The opposite position is more usual, i.e., a statistically significant effect is regarded as a positive treatment result regardless of whether the weight loss is so small that a clinical effect is probably absent[106]. Sometimes also the absence of weight gain and increase in BMI SDS is defined as a positive result[89].

These outcome goals must obviously be different for different degrees of obesity and at different ages and depending on whether obesity is caused by a hypothalamic dysfunction. For the moderately obese child, it may be sufficient to stop any further increase if the child is growing and BMI SDS is decreasing. But for the severely obese child, this is not enough. If the child is suffering from the disease obesity, another way to define an acceptable goal is to identify a weight loss that is associated with a reduction in risk markers for obesity co-morbidity. In three studies Reinehr *et al.* have demonstrated[70, 107, 108] a clinically significant decrease in negative health consequences for obese children after one year of behavioural treatment with a reduction of ≥ 0.5 BMI SDS units. This reduction led to improvements in cardiovascular risk factors, insulin sensitivity and all components in the metabolic syndrome. These findings have also been confirmed recently by Ford et al.[69].

2.2.6 Factors that affect the ability to benefit from treatment

It is important to note that interventions to reduce obesity may vary in effect depending on the age of the child and differences in metabolism, nutritional needs, physical maturation and psychosocial development throughout childhood. It is also very likely that the level of parental involvement will change with age and stage of development[95].

Low socio-economic status (SES) is seen more often in families with obese children than those with normal-weight children. Families with low SES have been shown to have a higher prevalence of social and psychological problems than the general population. This background perhaps contributes to the possibility of adapting the treatment[109].

Children suffering from various forms of mental disorders may have special difficulties with anti-obesity programmes involving behavioural modifications. This assertion is mainly based on personal experience since this aspect usually is not included in clinical trials. One study from Israel in 2005 found that 58% of the treated children suffered from ADHD[37]. This study is based on a small series (n = 32), but it should still be considered to be important; only 40% of the children had been diagnosed before the study despite the fact that all of them were followed by a clinician before the study. One possible reason for the non-diagnosis could be the diagnostic criteria, especially the hyperactivity. We have similar results from Stockholm[38]. One interesting issue for the future is how different genetic predispositions affect the ability to benefit from treatment.

2.2.7 Lost to follow-up

One major problem in obesity treatment in general is untimely stoppage of treatment by the patients. Large numbers of subjects who are lost to follow-up or drop out are presented regularly in all types of treatment studies, but not many studies address the problem specifically. Premature termination of treatment is often observed in child services. The Cochrane review reported a range of 12 to 52% after 12 months of treatment. Pinelli et al. reported a multicentre study in Italy with an attrition rate exceeding 90% [110]. A German multicentre study found follow-up data for 24% of the patients at 6 months, for 17% after 12 months and 8% at the 2-year follow-up. In 2010 Braet et al. published an interesting study of the topic in children and adolescents. Their results showed that drop-out was associated with increasing age, psychopathology in the children and poor motivation of the parents. They also found that non-completers more often reported the scheduling of the appointment and relevance of the treatment as barriers to completing treatment. The lost-to-follow-up patients did not differ with regard to gender, age, body mass index at baseline, parental BMI, socio-economic status (SES) or parental psychopathology[111].

It is important to study reasons for not completing treatment for several reasons[111]:

- The patients are not likely to receive the benefits of treatment.
- Premature termination will give feelings of failure and incompetence on the part of both the clinicians and the patients.
- Premature termination is often preceded by cancelled appointments and unannounced failures to show up. And this affects the service costs.
- When patients leave the centre prematurely, missed appointments contribute to delays in access to care for those already waiting for treatment.
- And most important, if we want to stop the obesity epidemic, enhancing treatment compliance will improve the effectiveness of the treatment and thereby reduce the negative medical and psychosocial consequences of childhood obesity.

2.3 NATIONAL CHILDHOOD OBESITY CENTRE

The National Childhood Obesity Centre is a referral centre for children with severe obesity. The children are enrolled nationwide. The primary goal is to help families to understand the severity of the disease and the need for lifetime treatment. The treatment consists of behavioural treatment, individually and in groups, low and very low calorie diets, pharmacological treatment using Orlistat® and/or Sibutramine® and surgical treatment. Patient safety is ensured by using these treatments exclusively in controlled studies. Our clinic was the first one in Sweden using this approach and started to treat obese children in 1997.

The clinical visits have a decision-making objective, whereupon the patients are referred to other clinical personnel for follow-up and motivational support. The objective of the treatment is to help/support patients to adopt more healthful eating habits, become more physically active, and reduce time spent in sedentary activities. Changes are encouraged to be made stepwise, based on present behaviours. The overruling principle was that the treatment should be intensified if it failed. This means that if the results were poor (weight gain), more frequent visits were prescribed. Therefore, the frequency of weight controls varied from weekly to once a year. The goal was that the patients should remain in treatment for at least five years regardless of the results.

The group therapies were given in Weight School, Summer Fat Camp with pool and resistance training.

The Weight school was held weekly with one-hour classes from 1998 to 2001 in the evening at the hospital during 12 to 16 weeks. The children attended classes divided into two age groups one children's group (aged 7-12 years) and one adolescent group (aged 12-18 years). These classes included short lectures on, for example, food know-how, food choices and the importance of physical activity, group discussions and practical exercises such as documenting food intake and demonstration of food alternatives and serving sizes. A health pedagogue and a dietician gave the lectures.

The Summer Fat Camp; An obesity camp for adolescents was started in 2001, designed as a two-week treatment programme with scheduled physical activities and strict meal orders. The programme included seminars on the consequences of obesity, the importance of physical activity and food know-how. The camp also included activities aimed at improving self-esteem.

Water and resistance training has been given in weekly one-hour classes during the school terms since 1998 and still, lead by the leadership of physiotherapists at the hospital. The subjects in the water-training programme were divided into two groups, by age. The resistance training was only available for adolescents.

When patients do not apply for follow-up visits, immediate contact is taken with the family, first by proposing a new visit and after that by telephone calls and letters to the caregiver. The target follow-up time for treatment duration is five years.

2.4 NATIONAL HEALTH CARE REGISTER FOR CHILDHOOD OBESITY (BORIS)

BORIS is a national web-based register for childhood obesity treatment which was started in 2005 (www.e-boris.se). It is supervised and supported by the Swedish Association of Local Authorities and Regions and the Swedish National Board of Health and Welfare. The purpose of the register is to follow all obese children during treatment in Sweden. Furthermore, it evaluates different methods of treatment for children at different ages, severity of obesity/ sex/other distinguishing factors, treatment and follow-up. The register gives us the opportunity to study change over time – i.e. are we getting better at treating childhood obesity? BORIS is therefore a good source for clinical research and quality assurance of obesity treatment, regionally and nationally.

3 AIMS

General aims

The overall aim of this thesis was to evaluate different forms of childhood obesity treatment primarily for severely obese children and adults and to study different factors of importance for the outcome of treatment.

Specific aims

I aimed to evaluate the demographic and other patient characteristics correlated with the efficacy of long-term behavioural obesity treatment:

- To study whether age at onset of obesity treatment affects treatment efficacy, defined as a decrease in BMI SDS.
- To study how the degree of obesity at the start of treatment predicts treatment efficacy.
- To study whether socio-economic factors, parental obesity or age at obesity onset affects the long-term treatment efficacy.
- To identify factors correlated with the subject's risk of being lost to follow-up.

Furthermore, to evaluate pharmacological therapy for severely obese children:

- To study whether children could handle and understand the necessity of a low-fat diet to reduce gastrointestinal problems during Xenical® treatment and whether the treatment affected physical and psychological well-being.
- To determine whether children suffering from hypothalamic or simple obesity together with syndromes that aggravate this condition can benefit from treatment with Reductil®.

4 MATERIAL AND METHODS

All children participating in these studies were patients at the National Childhood Obesity Centre. Treatment was initiated between January 1998 and January 2007. The patients in Studies III and IV are only patients in the respective studies because previous pharmacological treatment was an exclusion criterion in Studies I and II. Children in Study IV are not patients in Study III because the aggravating syndromes were excluded in Study III. A summary of the participants in study I-IV is presented in Table 1.

Table 1. Participants in Studies I–IV.

	Participants	Girls	Boys	Age	BMI	BMI SDS Karlberg	BMI SDS Rolland-Cachera
	n	n	n	min-max	mean	mean (min-max)	mean (min-max)
Study I							
Children	555	272	283	6-17	32.8	3.4 (1.6-6.1)	5.7 (1.8-11.5)
Reference children	36	17	19	6-10	25.4	3.3 (2.3-4.3)	5.8 (5.0-8.0)
Study II							
Children	643	313	330	6-17	33.0	3.4 (1.6-6.1)	5.7 (1.8-11.5)
Study III							
Children	11	7	4	8-12	32.8	3.7 (3.2-5.0)	6.3 (5.3-9.2)
Study IV							
Children	50	26	24	7-20	35.0	3.5 (2.2-5.4)	5.7 (2.9-10.0)

The group of reference children consists of children followed in the STOPP Study[112].

4.1 STUDY DESIGN AND PARTICIPANTS

4.1.1 Study I

To identify factors of importance for succesful weight loss during behavioural treament we followed longitudinally all patients referred to the National Childhood Obesity Centre between January 1997 and December 2004. Only patients undergoing behavioural treatment were included. Patients with other treatments (VLCD/LCD, drugs and surgery) and other diagnoses (syndromes, craniopharyngioma, Down's syndrome, myelomeningocele, various types of mental and psychological disorders) and children < 6 and > 17 years old at inclusion were excluded. The remaining children were divided into three age groups depending on age at onset of obesity treatment (6–9, 10–13 and 14–16years old).

All data in Study I were obtained from the BORIS Registry, data from a total of 684 children being collected from the registry. Of these 648, 129 failed to meet the inclusion criteria and were therefore excluded from further analyses see Figure 1.

To be able to contrast the effect of behavioural treatment of the youngest age group from spontaneous changes, data from 36 obese (BMI SDS > 5) children (mean age 8.5 yrs, range 6.4–10.3 yrs and BMI SDS mean 5.8, SD 0.9), followed during one to three years were used. Twelve (mean age 8.5 yrs, range 6.5–10.2 BMI SDS, mean 6.2, SD 1.2) of them were followed for three years. The children participated in the obesity prevention study STOPP[112] and data on children in both the intervention and control groups were used.

No intervention effect was reported in obese children and the children could therefore be pooled. This reference group consists of all children in the STOPP study who, during the first year, were classified as obese without any known obesity treatment.

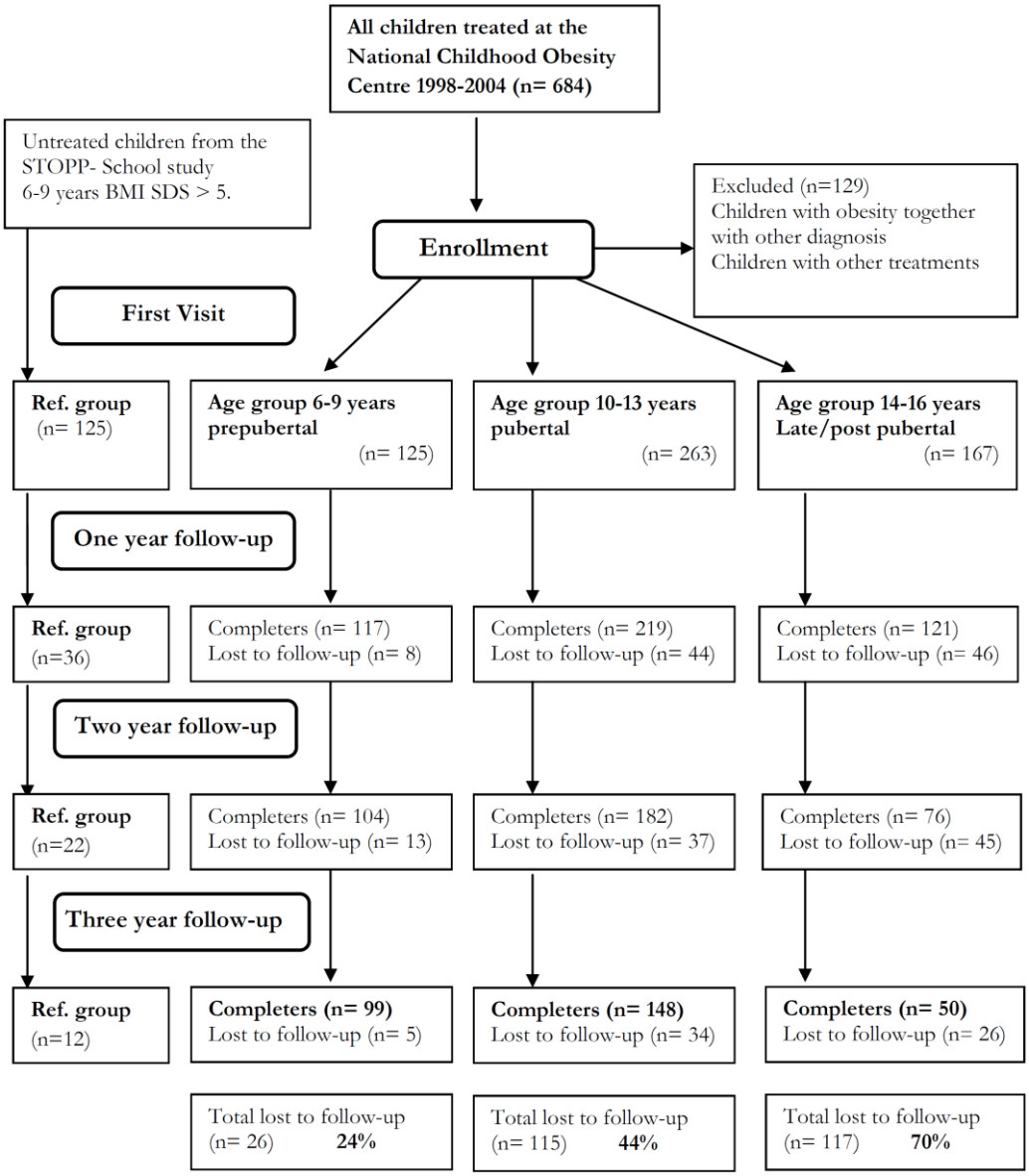

Figure 1. Flowchart of patients in Study I. The reference children consist of a subgroup from the STOPP Study[112]. All data are extracted from the quality register BORIS.

4.1.2 Study II

The aim of Study II was to investigate whether the degree of obesity when the behavioural treatment was initiated affects treatment outcome. Study II was based on a later and thereby larger sample of subjects than in Study I. All subjects were treated at the National Childhood Obesity Centre between January 1998 and December 2006. All data in Study II were obtained from the BORIS Registry. Initially, data on 966 children were obtained. Of these, a total of 323 failed to meet the inclusion criteria and were excluded from the study, see Figure 2.

The subjects were divided into three age groups, defined by age at the start of behavioural treatment. The age groups formed were the same as in Study I, i.e., 6–9.9 (prepubertal), 10–13.9 (pubertal) and 14–16.9 (late/post-pubertal) years. The children were further divided into two groups depending on degree of obesity, as moderately obese, BMI SDS < 3.5-1.6, and severely obese, BMI SDS ≥ 3.5.

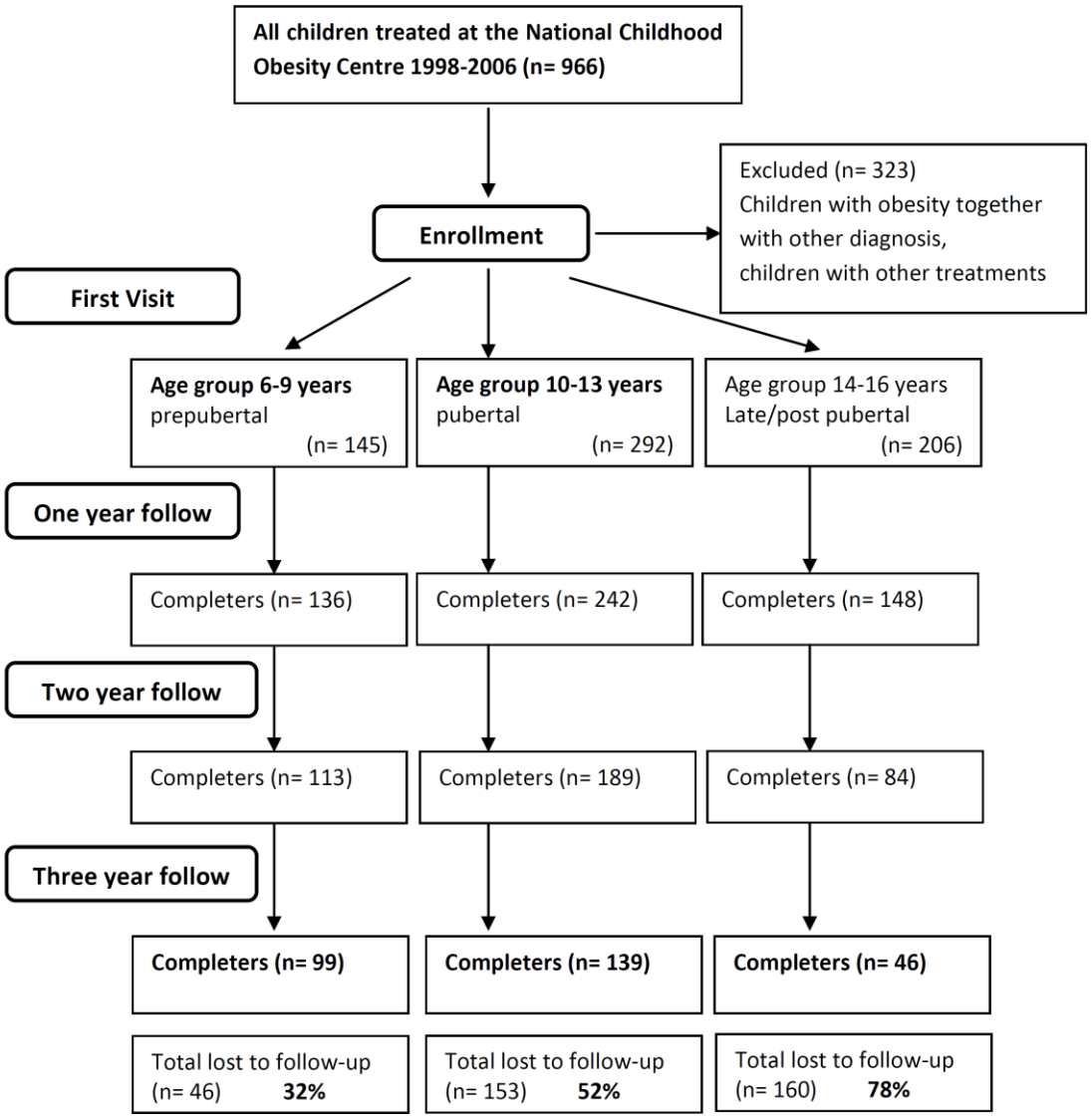

Figure 2. Flowchart of patients in Study IV.

4.1.3 Study III

This study was primarily designed to evaluate whether orlistat was a feasible treatment for obese prepubertal children with regard to tolerance, safety and psychological well-being. More specifically, we wanted to know if children in this age group could understand and handle orlistat without getting loose stools and thereby a reduced quality of life. These questions were expected to be answered without a control group.

The children were recruited for a 12-week open treatment; they received the standard adult dose of Xenical®, 120 mg, together with each meal three to four times per day. All children and guardians received detailed information regarding sources and recommended intake of dietary fat before the start of treatment.

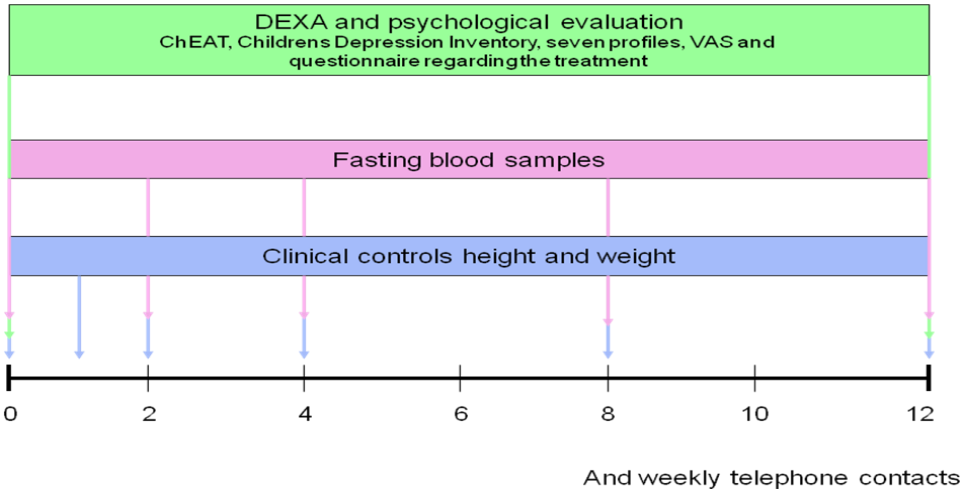

Figure 3. Study design for patients in the Orlistat Study.

The patients were investigated at the clinic before and after 1, 2, 4, 8 and 12 weeks of treatment, in addition to weekly telephone contacts. The visit controls consisted of weight and height checking. Blood chemistry was done before and after 4, 8 and 12 weeks of treatment. Body composition (DEXA) and psychological evaluation were done before and at the end of treatment, Figure 3.

Inclusion criteria's for this study were:

- Prepubertal children aged 7-12 yrs with:
- Primary obesity and BMI SDS > 4 (ref R-C)
- No other syndromes or disorders.

Twelve healthy, severely obese children were asked to participate in this study. One child dropped out before the start of treatment because of the required blood sampling. Eleven children, median age 11 years and BMI SDS 6.33, 4 boys and 7 girls, started and continued 12 weeks of treatment.

4.1.4 Study IV

To be able to determine if children who find it difficult to benefit from behavioural modifications due to hypothalamic obesity (CNS damage, LMBB, PWS and MC4R) and obesity with aggravating syndromes (Down's, MMC and MR/ADHD/ASD) can benefit from treatment with sibutramine. We conducted a randomised double-blind placebo-controlled cross-over study for 20 plus 20 weeks plus a 28-week open phase, see Figure 4. The families were also encouraged at all visits to make as many lifestyle changes as possible in their daily life.

The sibutramine dose required for these children was unknown. To see if there was any sibutramine resistance in the children suffering from hypothalamic disorders and to provide for them the best effect during the study period, we added a dosage increase. Therefore, all children started with 10 mg, per os, once daily and a dose increase to 15 mg, per os, once daily after 8 weeks if the weight loss was less than 4 kg, i.e 0.5 kg per week.

All patients were randomised in pairs, the purpose of matching the children two and two being to offset to some extent the risk that the first and second phase of treatment would not be comparable. In this way we ensured that an approximately equal number of children in each diagnostic group were given a placebo in the first and second treatment cycles.

The drug was distributed in new capsules in order to achieve blinding. The Apoteket Production and Laboratory (APL) facility in Stockholm was responsible for the production, labelling, packaging and randomisation.

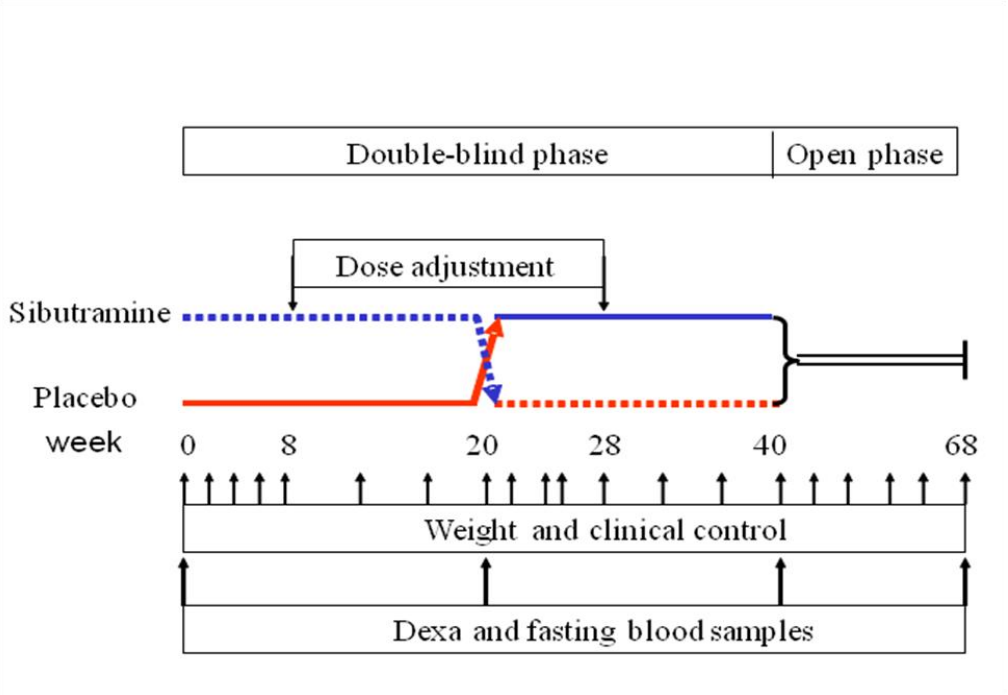

Figure 4. Study design for patients in the Sibutramine Study.

All enrolled children were patients at the National Childhood Obesity Centre. The patients were between 5 and 20 years of age and the BMI SDS was >3 according to Rolland-Cachera et al.[4]. The hypothalamic group of children were children diagnosed with having a defined syndrome for which obesity is a definitive criterion or with damage to the CNS that causes obesity and children with a disease that makes behavioural treatment impossible. A subgroup of children, the non-hypothalamic group, consisted of children with mental retardation and/or ADHD and/or autism spectrum disorder (ASD). Thirteen of these children attended special schools/classes for mentally handicapped children. See Table 2.

One of the exclusion criteria was co-medication with high doses of psychoactive drugs. Nevertheless, five patients with well-managed and low doses of SSRI were included. To ensure safety and to allow early detection of serotonergic symptoms, these children and their parents were contacted by telephone once a week.

Table 2. Characteristics of patients in the Sibutramine Study.

Condition	n	Age, yr (min-max)	BMI SDS (min-max)	SSRI
Hypothalamic obesity				
CNS damage	10	9-19.6	3.0-6.9	2
LMBB	6	7.4-20.2	3.6-9.7	0
PWS	4	13.2-17.5	3.9-4.5	2
mMC4R	2	14.5-19.4	2.9-6.9	0
Non hypothalamic obesity				
Mb Down	3	11.6-17.6	4.0-6.6	0
MMC	4	7.6-18.2	4.0-8.9	0
MR/ADHD	21	7.0-17.0	3.8-10.0	1
Total	50	7.4-20.2	2.9-9.7	5

4.2 MEASUREMENTS

All measurements are intended to ensure, to assess the outcome and to evaluate the treatment and include anthropometry, BORIS data, BMI SDS estimates, biochemistry, body composition, blood pressure and psychological evaluation.

4.2.1 Anthropometry

All the children are weighed and measured at all the clinical visits at the hospital, regardless of study. At all visits trained nurse assessed height measurements (Ulmer Stadiometer, Ulm, Germany) and body mass (Vetek TI-1200; Väddö, Sweden) with the children wearing underwear and a lightweight shirt and without shoes.

The BMI SDS was calculated in the BORIS database using weight, height, age and gender based on two different references[4, 5]. Age at onset of obesity was derived from growth charts as the age at which the BMI exceeded iso-BMI 30, i.e., the BMI that corresponds statistically to an adult BMI of 30[3]. Parental BMI data in the BORIS database are based on the weight and height data reported by the parents at the first clinical visit.

4.2.2 BORIS data

The register comprises background and demographic characteristics of patients during treatment: gender, pubertal status, age at onset of obesity, development of weight over time, parental weight status, socio-economic status (parental occupation) and BMI SDS. Socio-economic status was defined in terms of parental occupation/education. This was coded, based on official Swedish socio-economic categories (SEI) and the Swedish Standard Classification of Occupations (SSYK) provided by Statistics Sweden (SCB), into three categories: (1) at least one parent with an academic degree, (2) at least one parent with a post upper secondary school education and (3) others (unemployed, early/disability retired, long-term sick-listed, students, housewives).

Patients who missed follow-up visits and those who refused to show up at visits after additional contacts were classified under three main causes of loss to follow-up: 1. Patient's/parents' decision to stop treatment; 2. Treatment goals achieved; or 3. External causes (such as patient moved, patient turned 18, no referral from a primary care physician).

4.2.3 BMI SDS estimation

The standard deviation scores of the BMI are based on two different populations. The first studied by Rolland Cachera et al.[4] with a data collection started in 1953 in a French population of children from one month (n = 494) to 16 year of age (n = 117). The second study was conducted by Karlberg et al.[5] on a Swedish population of children (n = 3650) born in 1973–1975.

The relationship between Karlberg and Rolland-Cachera was estimated using data from the STOPP Study[112] and the relation is a prescribed BMI SDS Karlberg = -0.17 + 0.89 x BMI SDS Cachera - 0.05 x BMI SDS Cachera^2 and is shown graphically in Figure 5. The visual inspection reveals that values between -2 and 2 are relatively similar, but values below -2 and above 2 are not interchangeable for comparisons between studies.

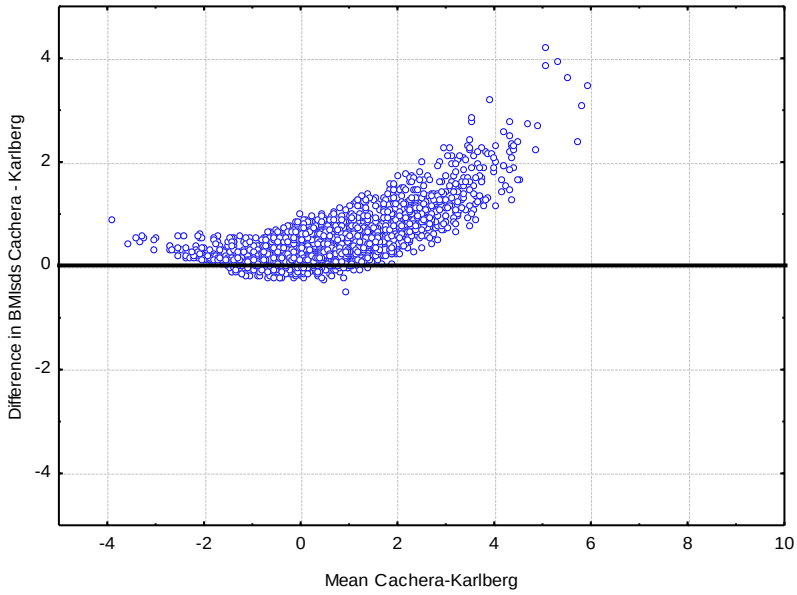

Figure 5. Estimation of relationship between BMI SDS Karlberg and Rolland Cachera.

4.2.4 Biochemistry

The blood sampling had two main objectives: in Study III to ensure that the child's continued growth and pubertal development follow the norm and to find unexpected and previously detected side effects. In both Study III and IV the blood samples were taken to ensure safety, but primarily to detect improvements during treatment.

Study III
This included gonadotropins (LH luteinising hormone, FSH follicle-stimulating hormone), testosterone, thyroid function tests (TSH thyroid-stimulating hormone, T4 free thyroxine and T3 free triodothyronine), liver function test (ALAT alanine aminotransferase, ALP alkaline phosphatase and gamma-GT glutamyltransferase), cholesterol, triglycerides, insulin, glucose, phosphate, uric acid, calcium, vitamin D (1,25-OH), vitamin A (retinol) and vitamin E (2α-tocopherol).

Study IV
This included fasting levels of glucose and insulin and non-fasting serum levels of cholesterol and triglycerides, as well as thyroid function tests (TSH thyroid-stimulating hormone, T4 free thyroxine and T3 free triodothyronine), liver functions test (ALAT alanine aminotransferase, ALP alkaline phosphatase and gamma-GT glutamyltransferase).

4.2.5 Body composition

Studies III and IV
To be able to determine if the children lost fat mass during treatment, we measured total body composition as a complement to BMI and BMI SDS. This was determined by dual-energy x-ray absorptiometry (DXA; Lunar DPX-L, version1.5E, and Prodigy programme version 1.x; Lunar Corporation, Madison, WI, USA). Results were expressed in fat mass (kg), and truncal fat percentage (%) and fat percentage of bodyweight (%).

4.2.6 Blood pressure

Study IV
The most common side effect of sibutramine treatment is increased blood pressure and heart rate. To ensure safety during the study with sibutramine the blood pressure was measured. Blood pressure was measured at the wrist while sitting after resting 10 minutes; EW3000; Matsushita CO., Kyoto, Japan. The patients were withdrawn from the trial if the systolic/diastolic blood pressure increased during the monitoring by 10 mm Hg or more at two consecutive measurements.

4.2.7 Psychological evaluation

Study III
To answer the questions about well-being during orlistat treatment, the evaluation by the psychologist included:

- A Swedish version of the Children's Eating Attitudes Test (ChEAT) measuring 'dieting', i.e. avoidance of fattening foods and body shape preoccupation; 'bulimia', i.e. bulimia and food preoccupation; and oral control, i.e. personal and social control of eating behaviour. The maximal total score is 78, and a score above 20 has been taken to suggest anorexia nervosa. The mean ChEAT score of randomly selected Swedish children in the fifth grade is 2.0 for girls and 2.5 for boys[113-115].

- I Think I Am, a Swedish test measuring school children's self-image[116].

- Swedish translation of the Children's Depression Inventory[117].

- Series of seven profiles of children with increasingly body shapes (girls and boys), Fig 6, shown by a psychologist to participants who were asked to indicate "This is how I look now" and "This is how I would like to look" [118].

- Estimations by the participants on a visual analogue scale (VAS) of how much they wanted to lose weight (0 = 'not at all', 100 = 'very much, more than anything else') and how difficult they thought losing weight would be or was (0 = 'not difficult at all', 100 = 'impossible').

- Questionnaire regarding the treatment examining eating and drinking habits, discomfort related to intake of the drug or clinical examinations, and who in the family had been responsible for ensuring that the drug had been taken properly.

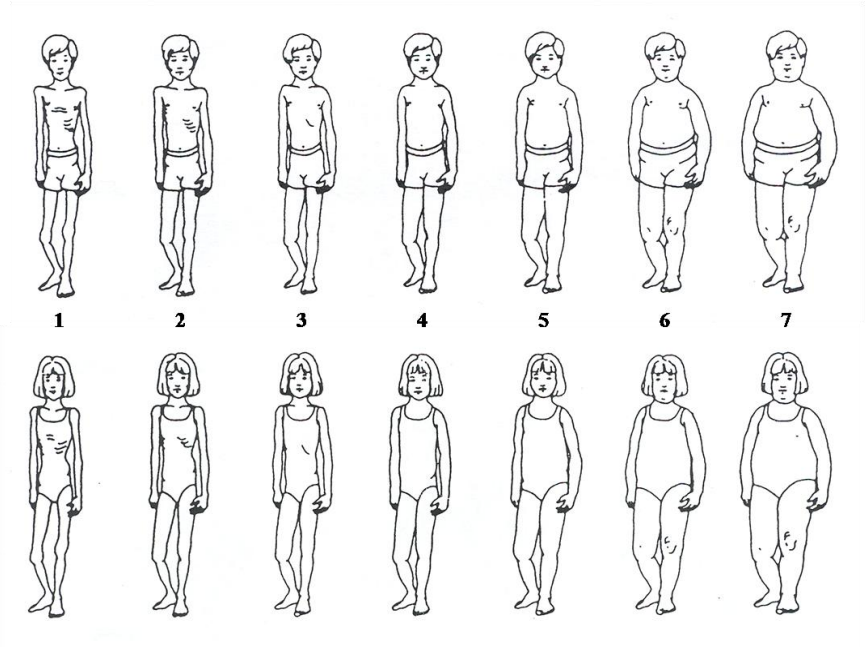

Figure 6. Series of seven profiles with increasingly body shapes.

4.3 STATISTICAL ANALYSES AND DATA HANDLING

Table 3. Statistical methods used in Studies I–V.

	Study I	Study II	Study III	Study IV
Descriptive statistics	x	x	x	x
Wilcoxon signed ranks test			x	
Friedman test			x	
Pearson correlation test			x	
ANOVA repeated-measures				x
ANCOVA	x	x		
Kruskal-Wallis	x			
Mann-Whitney	x			
Logistic regression	x	x		

The statistical methods used in this thesis are presented in Table 3. The standard deviation BMI scores are based on two different populations. The first conducted by Rolland Cachera et al.[4] of a data collecting started in 1953 in a French population of children from one month (n = 494) to 16 years of age (n = 117). The second conducted by Karlberg et al.[5] in a Swedish population of children (n = 3650) born in 1973–1975.

In study II missing data is replaced with the last observation carried forward method (LOCF).
In Studies III and IV two analysis populations were defined: first, the completers' population was defined as all children who were completely assessed for BMI SDS from the first visit throughout the three-year follow-up visits, i.e. observed cases (OC). Second, a full analysis population (FAS) was defined as all children who had a first visit. The latter is to be used for analyses to be interpreted as a sensitivity analysis for the analysis with the completers' population. In the full analysis population, missing data for patients lost to follow-up were replaced using (i) LOCF and (ii) the baseline value carried forward (BVCF).

The Pharma Consulting Group (Uppsala, Sweden) carried out all statistical analyses in Paper II.

4.4 ETHICAL APPROVAL

Studies I and II were approved by the Ethics Committe of Karolinska Institutet (Dnr. 2005/1231-31/2).
Study III was approved by the local hospital ethics board (Dnr. 322/98) as well as the Swedish Medical Products Agency.
Study IV was approved by the Ethics Committe of Karolinska Institutet (Dnr. 178/01 and amendment) and the Swedish Medical Products Agency.

5 RESULTS

5.1 STUDIE I AND II

These two studies are based on a large number of patients treated at the National Childhood Obesity Centre for at least three years. The major and most important finding is that it is possible to treat children with a robust behavioural with good results if the treatment starts at an early age. Age at start of treatment was the only success factor found in these two studies. Surprisingly, age at obesity onset, parental weight and the socio-economic factor were not of importance for the long-term effect.

5.1.1 Factors correlated with treatment efficacy

There are several factors that could influence treatment efficacy, shown in Table 4.

Table 4. Factors studied that could influence treatment efficacy.

Factors affecting treatment efficacy	Affect	May affect	No proven effect
Age at start of treatment	X		
Degree of obesity	X		
Gender		X	
Age at onset of obesity			X
BMI, mother		X	
BMI, father			X
Socio-economic status			X

Age at start of treatment

The numbers of children in the three age groups were 125 (age 6–9 years), 263 (age 10–13) and 167 (age 14–16). The mean BMI SDS on entering behavioural treatment (first visit) was 1.3 units higher in the 6–9 age group than in the 10–13 and 14–16 age groups ($P < 0.05$). The mean BMI SDS declined from the first visit to the three-year follow-up, ($P < 0.05$) and was related to age in the completers' analysis population. There was a significant interaction effect between age group and treatment duration ($P < 0001$), and post hoc analyses showed that the mean BMI SDS decline was greater in the youngest age group (6–9 years) compared to the other age groups ($P = 0.001$). On adjusting for baseline differences, the mean changes in BMI SDS from baseline/first visit to follow-up years 1, 2 and 3, respectively, were similar in size during each year with a statistically demonstrated stronger decline in the 6–9 age group. In the age group 14-16, the mean BMI SDS decreased during the first year ($P < 0.05$) but no decrease could be statistically demonstrated during follow-up years 2 and 3; see Table 5. After 3 years of treatment 19% of the children aged 6–9, 24% in age group 10–13 and 14% in age group 14–16 had changed from obese to overweight, corresponding to a BMI of 30 kg/m^2 at age 18.

	Completers			FAS, LOCF			FAS, BVCF		
	Age 6–9 n=73	Age 10–13 n=118	Age 14–16 n=37	Age 6–9 n=125	Age 10–13 n=263	Age 14–16 n=167	Age 6–9 n=125	Age 10–13 n=263	Age 14–16 n=167
First Visit mean (SE)	6.6 (0.2)	5.5 (0.1)	5.3 (0.2)	6.7 (0.2)	5.5 (0.1)	5.2 (0.1)	6.7 (0.2)	5.5 (0.1)	5.2 (0.1)
Year 1 mean (SE)	6.0 (0.2)	4.7 (0.1)	4.9 (0.2)	6.0 (0.1)	4.8 (0.1)	4.9 (0.1)	6.0 (0.2)	4.8 (0.1)	4.9 (0.1)
Year 2 mean (SE)	5.3 (0.2)	4.3 (0.1)	4.9 (0.2)	5.6 (0.1)	4.6 (0.1)	5.0 (0.1)	5.7 (0.2)	4.7 (0.1)	5.0 (0.1)
Year 3 mean (SE)	4.8 (0.2)	4.2 (0.2)	4.8 (0.3)	5.3 (0.1)	4.5 (0.1)	4.9 (0.1)	5.7 (0.2)	4.9 (0.1)	5.1 (0.1)

Table 5. The mean BMI SDS[4] (SD) for three different analysis populations: completers, LOCF (Last observation carried forward) and BVCF (Baseline value carried forward) during three years of behavioural treatment.

Degree of obesity

The numbers of severely and moderately obese in each age group were 91 and 54 (age 6–9 years), 98 and 194 (age 10–13) and 82 and 124 (age 14–16), respectively. In children with lower initial levels of BMI SDS (<3.5), the youngest age group had a marked decline in BMI of SDS at the first, second and third year. Treatment efficacy was less pronounced in the older age groups. In children with higher initial levels (> 3.5) the same pattern was observed, but children in the oldest age group showed no change in BMI SDS after one, two or three years see Figure 7.

Gender

There was no difference between boys and girls with regard to patterns in the mean change in BMI SDS. Analyses using the last observation carried forward (LOCF) method for replacement of missing data did not alter these results in Paper III. When we divided the larger material in Papers IV we found in the age group 10–13 years, the subgroup of severely obese boys had a significant larger mean (SD) decrease in BMI SDS after three years (-0.5 (0.6) than girls (-0.1 (0.6), $P < 0.001$) on applying LOCF analyses. The pattern was similar when analysing completers only, but the differences did not reach statistical significance. Gender differences were not observed in any other age group.

Heredity, mother's and father's BMI

The prevalence of overweight and obesity among the parents was 59% in the fathers and 57% in the mothers. In Paper III the parental BMI status did not influence the effect of treatment. When we divided the children above and below BMI SDS 3.5 and examined if the effect of parental BMI status on treatment efficacy differed we found that the severely obese children with normal-weight mothers showed a larger mean (SD) decrease in BMI SDS compared to those with obese mothers (-0.3 (0.6), $P = 0.04$). We could not detect any relation between their fathers' weight status and change in BMI SDS during treatment.

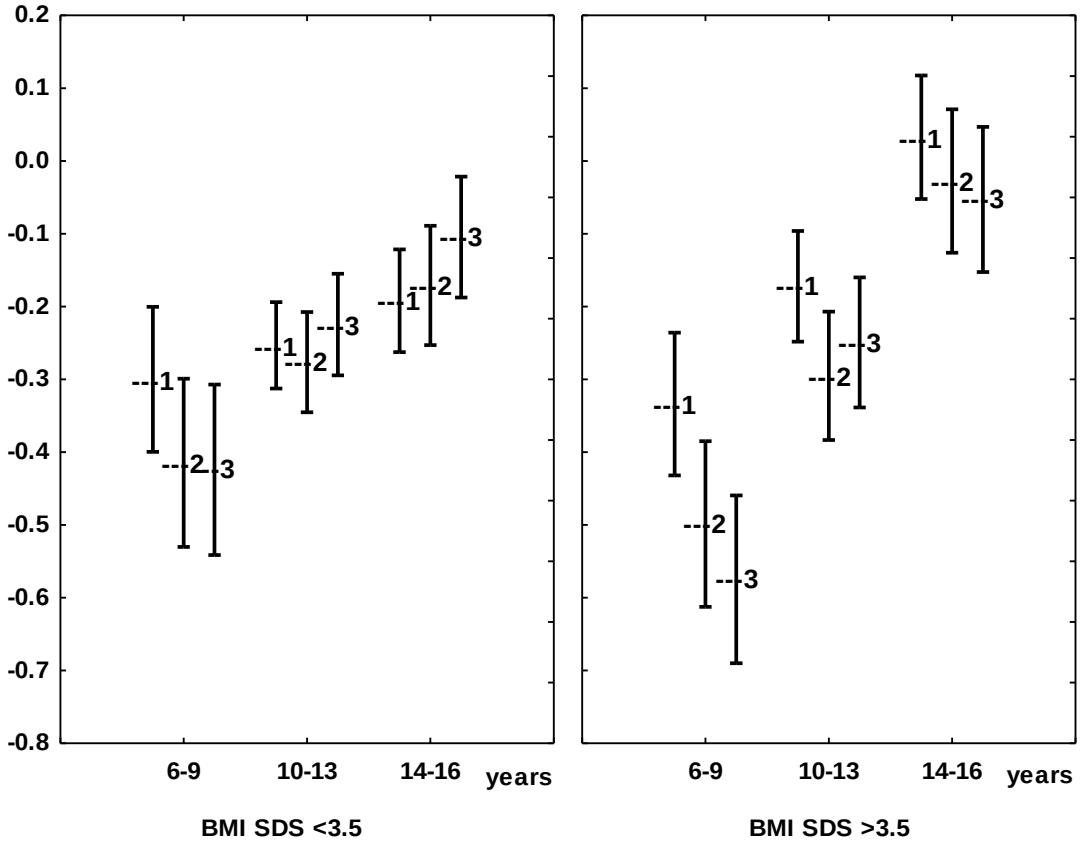

Figure 7. Change in BMI SDS as an effect on age at start of treatment in children with BMI SDS above and under 3.5, respectively. Changes in BMI SDS during years 1, 2 and 3. Values are adjusted for differences in BMI SDS at the start of treatment.

5.1.2 Relation between treatment efficacy after one and three years of treatment

When we analysed the change in BMI SDS from baseline to the one-year follow-up and from baseline to the three-year follow-up we found only a weak correlation, $r = 0.51$ ($P < 0.001$), Figure 8. Among children showing no response, i.e. no numerical decrease in BMI SDS after one year of treatment, 15 out of 18 in the 6–9 age group, 4 out of 16 in the 10–13 age group and 3 out of 12 in the 14–16 age group showed a clinically relevant response of an at least 0.5 unit decrease in BMI SDS at the end of year three.

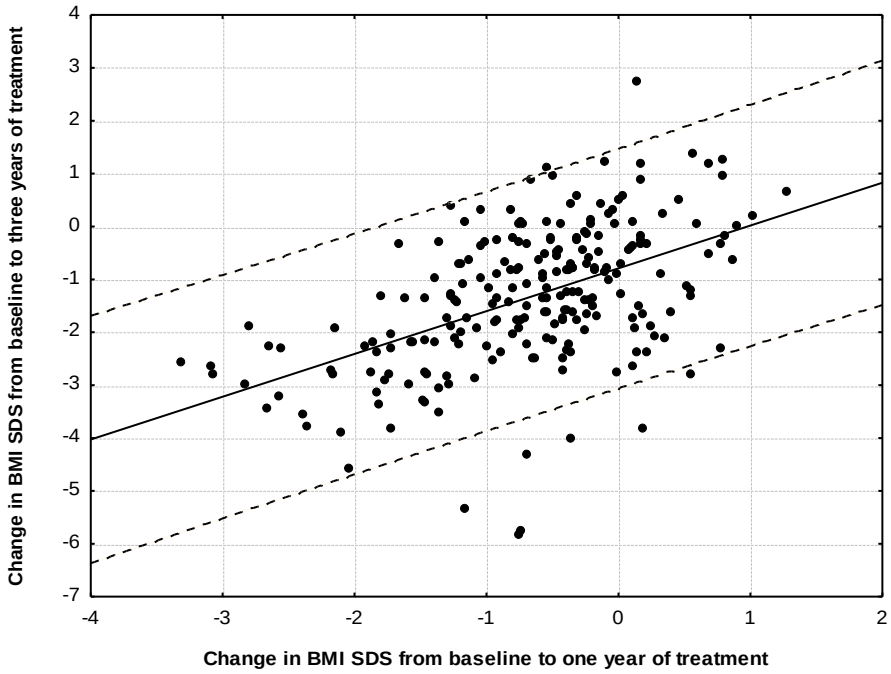

Figure 8. Correlation between changes in BMI SDS from baseline to one-year follow-up (x-axis) and from baseline to three-year follow-up (y-axis). As shown by the prediction intervals, only limited information on the three-year outcome can be drawn from the results of one year of treatment.

5.1.3 Prediction of the outcome based on age at onset of treatment

As a tool for clinical decision-making before the initiation of treatment, we calculated the expected result based on patient age at baseline, i.e. the proportion of subjects achieving a clinically relevant decrease in BMI SDS (> 0.5 and > 1.0, respectively) from baseline to year 3. This association is illustrated in Figure 9.

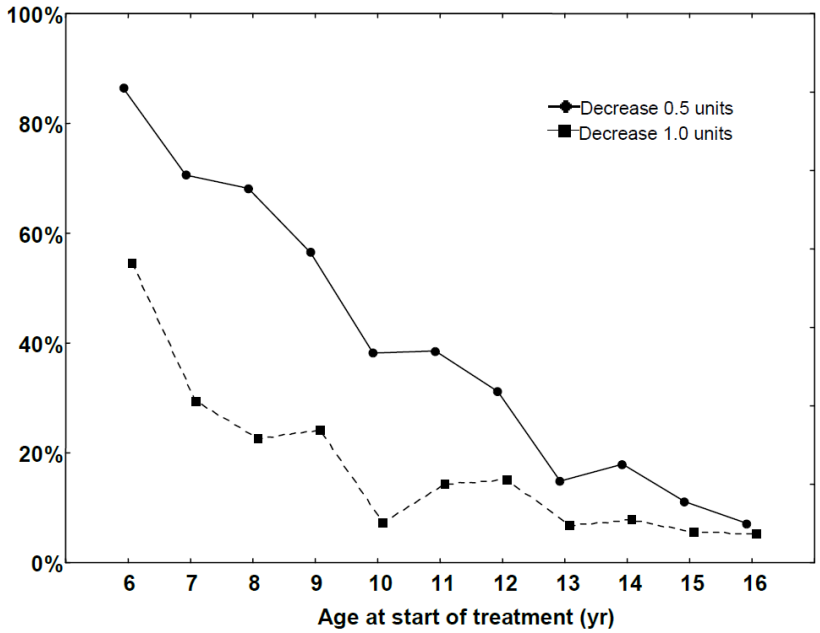

Figure 9. Percentage of subjects who achieved a reduction of 0.5 and 1.0 BMI SDS unit after three years of behavioural treatment. Analyses performed using the last observation carried forward methods. Number of individuals age 6 yrs, n=22, 7 yrs, n = 17, 8 yrs, n = 44, 9 yrs, n = 62, 10 yrs, n = 55, 11 yrs, n = 70, 12 yrs, n = 93, 13 yrs, = 74, 14 yrs, n=78, 15 yrs, n = 72, and 16 yrs, n = 56.

In further regression analyses using the LOCF method for replacement of missing data, age was found to be a significant predictor of a decrease of 0.5 BMI SDS unit (OR = 0.68 per year, P < 0.001). Analyses using subjects with complete cases showed similar results. The corresponding odds ratio for age for predicting a decrease of 1.0 BMI SDS unit or more during three years of treatment was 0.81 per year (P = 0.001) using the LOCF method for replacement of missing data and 0.90 per year (P = 0.10) when using the complete cases population.

The second important finding is the high rate of drop-outs, especially in the adolescent group of children.

5.1.4 Factors correlated with patients lost to follow-up.

There are several factors that could influence the frequency of patients lost to follow-up, shown in Table 6.

Table 6. Factors studied that could influence the frequency of patients lost to follow-up

Factors affecting drop-outs	Affect	May affect	No proven effect
Age at start of treatment	X		
Degree of obesity			X
Gender			X
Age at onset of obesity			X
BMI, mother		X	
BMI, father			X
Socio-economic status		X	

Age at start of treatment

A large number of subjects were lost during the treatment period, and only 30% of the adolescents who initiated treatment at age 14–16 remained in treatment at the year-three follow-up. There were 52 children in age group 6–9, 145 in age group 10–13 and 130 in age group 14–16 who dropped out during the follow-up period. The major reason for loss to follow-up was the patient's/parents' decision to stop treatment. Age was thus strongly related to the risk of dropout. Patients in age groups 10–13 and 14–16 exhibit an odds ratio for loss to follow-up of 1.79 ($P = 0.009$) and 5.19 ($P < 0.001$), respectively, compared to the 6–9 age group, the reference group.

Heredity; mother's and father's BMI

We found a trend towards an increased risk (OR = 1.51, $P = 0.09$) of being lost to follow-up for children with normal-weight mothers compared to children with obese mothers. No statistically demonstrated effect of the father's weight status on the risk for being lost to follow-up was found.

Socio-economic status

Families with at least one parent with an academic degree showed a trend towards a lower risk (OR = 0.65, P = 0.07) of being lost-to-follow-up than families with no academic degree.

5.2 STUDY III

This pilot study of orlistat treatment in prepubertal children indicates that the children were able to comply with the treatment and adapt food intake to minimise side effects. The side effects were mild and tolerable and the median weight loss was 4 kg. All children and guardians expressed an interest in continuing the treatment after the study period. This study was the first to evaluate the effects of orlistat in prepubertal children and there are still no other published studies in this age group.

The evaluation of participants with ChEAT demonstrated increased awareness of food alternatives and the need to make choices. The median total score increased from 7 to 10 (P = 0.011). The median score reflecting 'dieting" increased from 3 to 5 (P=0.041) and the score reflecting 'oral control' from 3 to 4 (P = 0.034), while the score reflecting 'bulimia' did not change. There was no indication of clinical depression before or after treatment. The treatment resulted in a non-significant trend towards improved self-image. After treatment, the children identified their own physique with a thinner silhouette. Most importantly, they perceived losing weight to be less difficult after treatment, and there was a non-significant trend towards increased motivation to lose weight. This is shown in Table 7.

Table 7. Psychological evaluation of the participants.

	Before	After	P
Eating attitudes (n=11)	7 (2-11)	10 (5-19)	0.011
Self image (n=10)	5 (3-9)	5 (3-9)	0.059
Depression inventory (n=11)	5 (0-14)	5 (0-13)	0.438
Self estimation of body shape (n=11)	6 (4-7)	5.5 (4-6.5)	0.020
Desires body shape (n=11)	4 (3-5.5)	4 (3-6)	0.783
Motivation to lose weight (n=10)	99 (50-100)	100 (70-100)	0.078
Estimation of difficulties (n=10)	50 (15-90)	50 (0-90)	0.043

Data are shown as median (range).

All children reported orange, oily stools after high fat intake. Two children reported frequent diarrhoea; these two children showed only a minor BMI change indicating that they and/or the parents were unable to reduce the fat intake.

There were no significant changes in fasting insulin and glucose, but vitamin E (P = 0.028), vitamin A (P = 0.028) and gamma-GT (P = 0.003) were lower at follow-up. Vitamins E and A showed a minor U-shaped variation profile during the study period. There was a significant decrease in gamma-GT after treatment, within the normal range, while the levels of ALAT and ALP were unaffected.

The median weight loss was 4 kg, ranging from a reduction of 12.7 kg to an increase of 2.5 kg (P = 0.016). Percentage body fat changed from 48.9% to 45.9% (P = 0.008). The weight reduction was highly correlated with change in body fat ($r = 0.953$, $P < 0.001$). All patients completed the 12-week treatment.

5.3 STUDY IV

Treatment with sibutramine in both the first arm (starting with sibutramine) and second arm (starting with placebo) caused a significant decrease in BMI SDS compared with the placebo ($P < 0.001$). This decrease in BMI SDS was approximately the same (0.7 BMI SDS); see Fig 10.

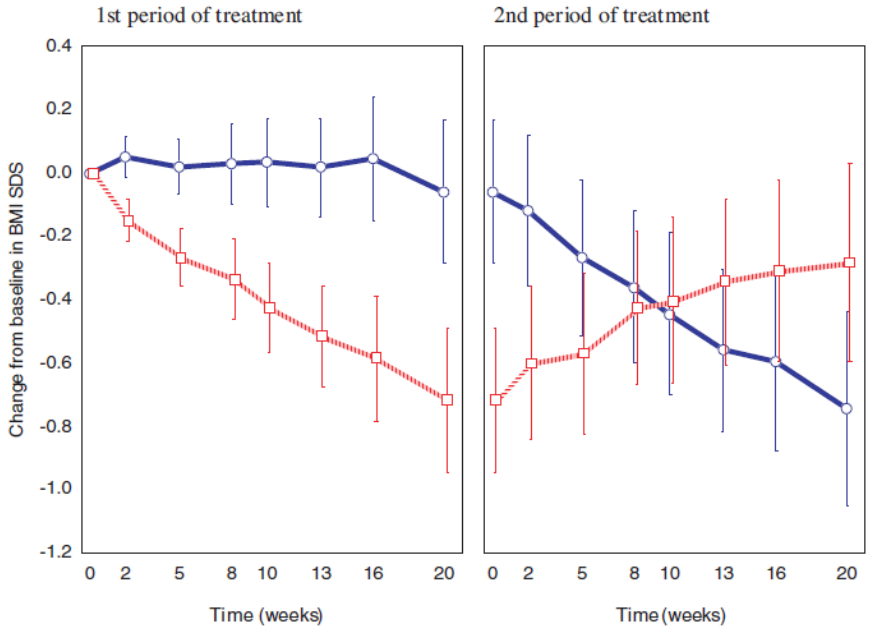

Figure 10. Effects of sibutramine or placebo on the BMI SDS of patients during the blinded phase of the study. Twenty-four patients (solid blue line) received the placebo during the first period of treatment and sibutramine during the second period and 25 patients (dotted red line) initially received sibutramine. The data presented are means and 95% confidence intervals.

To examine whether children exhibiting hypothalamic obesity were resistant to the weight-lowering effect of sibutramine, these subjects ($n = 19$) were compared with the children with non-hypothalamic obesity ($n = 26$). As seen in Fig 11, both the subgroups with hypothalamic ($P = 0.005$) and non-hypothalamic obesity ($P = 0.001$) showed significant reductions in weight while receiving sibutramine in comparison to placebo. However, the effect of sibutramine on the subjects with non-hypothalamic obesity was more pronounced, indicating that hypothalamic obesity is associated with partial resistance to this drug.

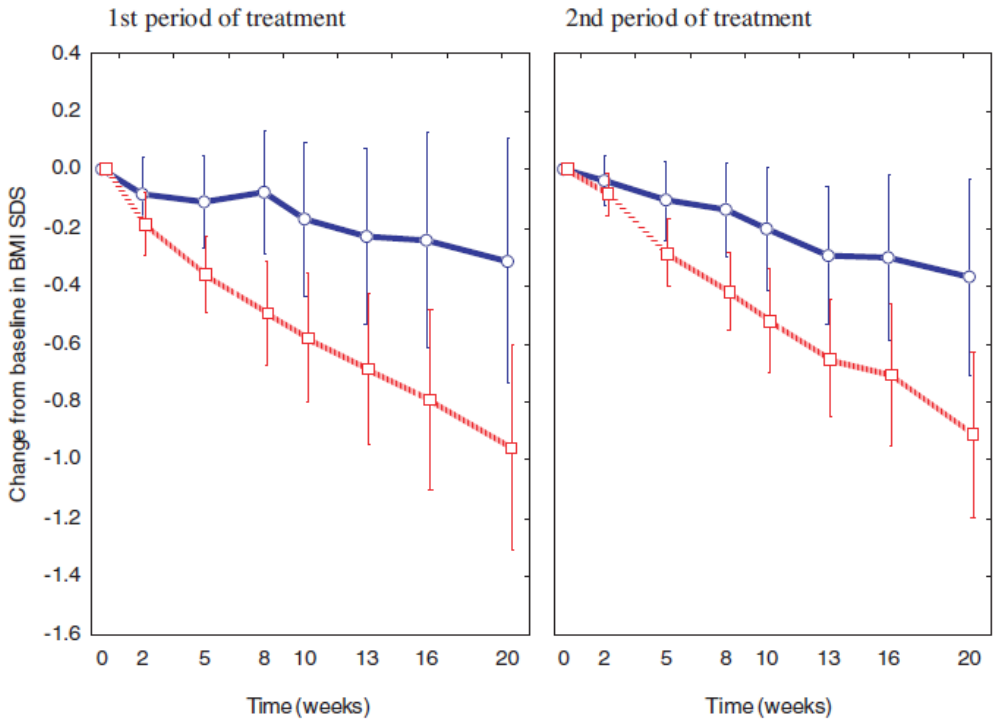

Figure 11. Comparison of the effects of sibutramine treatment on children with hypothalamic (solid blue line) and non-hypothalamic (dotted red line) obesity. The data presented are means and 95% confidence intervals.

Children requiring an increased dosage after eight weeks of sibutramine from 10 to 15 mg comprised 94% in the hypothalamic group and 66% in the non-hypothalamic group. This dose increase showed no significantly enhanced response (P = 0.51). The response to sibutramine was linear with time.

During the open-study phase, a continuous reduction of weight was observed. The same pattern was observed for those who received placebo or sibutramine first in the blinded phase. However, the rebound effect observed during placebo treatment of the subjects who initially received sibutramine was not followed by any pronounced reduction in weight when these same individuals again received the drug. The total reduction for the group that was initially administered the placebo, and was therefore treated with the drug for 48 consecutive weeks, was approximately 1 BMI SDS unit. For the group receiving sibutramine in the first blinded phase, the final outcome was less beneficial. Apparently, for this type of patients, continuous treatment with sibutramine may be more beneficial than intermittent administration.

In addition to decreased plasma levels of triglycerides (P = 0.04) during the placebo-controlled phase of this study, no other blood samples (cholesterol, insulin and glucose) were significantly changed.

The total body fat percentage was decreased by treatment with sibutramine compared with placebo (change during sibutramine treatment from 48.6 ± 1.3 to 46.7 ± 1.4% and during placebo from 47.9 ± 1.3 to 47.8 ± 1.4%, P = 0.003). After the open phase the total body fat percentage had decreased further to 44.0 ± 1.9%, P = 0.01.

Reported adverse events during the placebo-controlled and the open phase of the study were constipation, xerostomia, fluctuations in mood, insomnia and fatigue. The numbers of patients who demonstrated adverse effects were similar among those receiving the placebo and those receiving sibutramine. The blood pressure and heart rates of the patients in both groups varied considerably, but no differences in means were observed. Six serious adverse events were reported, all when the child received placebo: two children exhibited signs of depression, three suffered tumour recurrences and one developed type 2 diabetes.

Despite the contraindication for the use of SSRI drugs and sibutramine, five such patients were included under strict control in this study. To ensure safety and to detect possible adverse serotonergic events as early as possible, the study nurse maintained weekly contacts with the families. However, no adverse events were observed.

Forty-five patients (90%) completed the randomised, double-blind phase. Three subjects with hypothalamic obesity were withdrawn due to tumour recurrence and two with non-hypothalamic obesity failed to comply satisfactorily. During the open-study phase, another three subjects withdrew from the study: two with ADHD/mental retardation refused to take the drug and one patient with hypothalamic obesity was referred to a psychiatric clinic for severe illness.

6 DISCUSSION

6.1 DISCUSSION OF RESULTS

The results from this thesis provide several answers but also leave us with many questions to discuss.

6.1.1 Age at start of treatment

The effect of behavioural treatment varied considerably. Some children normalised their BMI whereas other children had an increased BMI SDS after three years. However, age at start of treatment was the only independent factor related to treatment success. This finding is in line with previous follow up studies of short-term behavioural treatment programs[106, 119, 120] . These findings might be seen as self-evident since the younger children have had a shorter period of time in life when they learned poor eating and lifestyle habits, and greater opportunity for parents and other relatives to influence. It can also be questioned whether the decline in BMI SDS is a treatment effect or if it is primarily regression to the mean that affects young children.

However data from the STOPP study clearly indicates that the observed decline in BMI SDS was a treatment effect since the obese children in the STOPP study had a negligible excess weight loss.

Despite that the behavioural treatment is more effective among young children, treatment of young obese children is rare in Sweden. In the Swedish National Health Care Register for Childhood Obesity, BORIS, the average age for treatment start is 10.2 years in entire register (n=6491) for the year 2011. The trend indicates declining age at start of treatment but it is still too high, Figure 12. In paper II we can see that it is possible to reach a clinical important reduction of 0.5 BMI SDS units in 40 % after three year of treatment in patients aged 10 yrs. If treatment is initiated at age 7, 70% could expect such a weight loss.

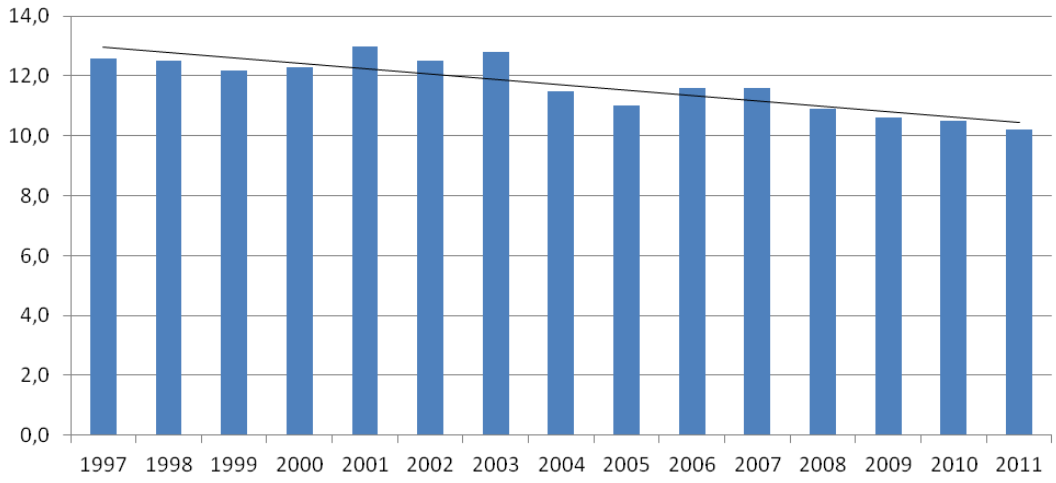

Figure 12. Age at start of treatment of all children registered in BORIS from 1997 to 2011.

One of the most important tasks is therefore to identify these obese children and initiate early treatment from 6-7 years of age to reduce the number of severely obese adolescents in need of pharmacological and/or surgical treatment. Of the severely obese adolescents in paper II 92% were already overweight and obese at age seven Figure 13. BMI SDS 2.3 is an approximate limit for obesity in calculations based on Karlberg BMI SDS[5].

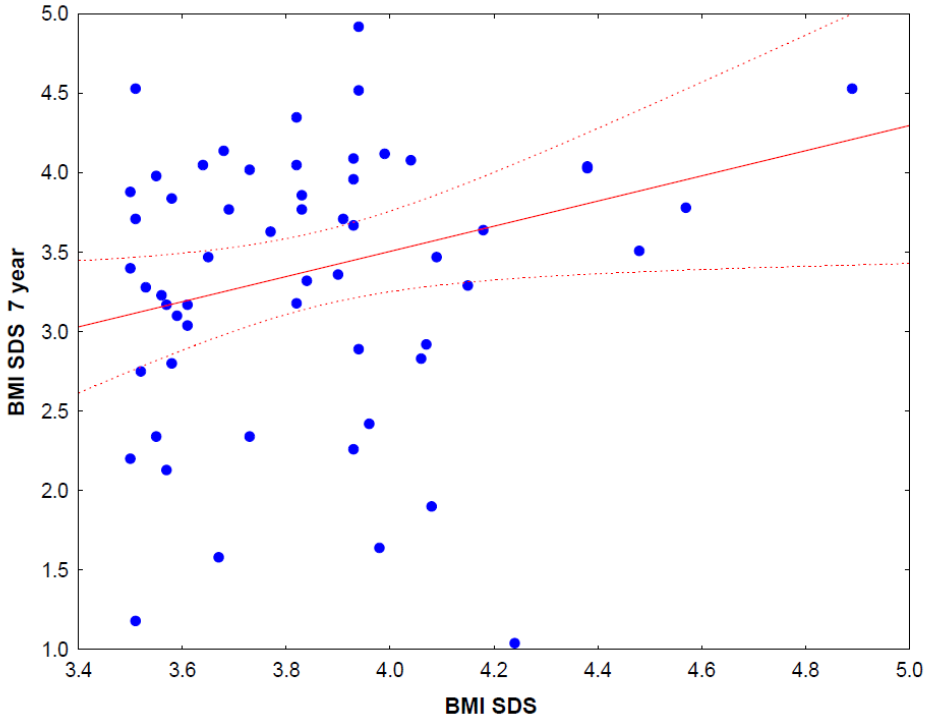

Figure 13. Degree of obesity at age seven for all severe obese adolescents 14-16 year at start of treatment in work II n=82.

6.1.2 Who are the lost to follow up patients?

Poor attendance is a major challenge in all obesity treatment both in children and adults. It is maybe even more difficult to find the typical characteristics of the patients lost to follow-up in childhood obesity due to that the children are also influenced by the parents and other care givers characteristics, problems and needs. Despite that the dropout rate is high this is an insufficiently explored area and those who have tried reported that the degree of obesity at treatment onset was the only factor of importance for retention rate[121, 122]. When analyzing lost to follow up among the children in paper two, we could see that the degree of lost to follow up was slightly but significantly higher in the severely obese group but quite similar, Table 8.

Table 8. Percentage of children lost to follow-up by treatment year.

BMI SDS < 3.5 at start of treatment			
First visit	6–9 years n=54	10–13 years n=194	14–16 years n=124
Lost during year 1	9%	19%	24%
Lost during year 2	9%	18%	32%
Lost during year 3	9%	16%	19%
Total lost to follow-up	28%	52%	75%
BMI SDS > 3.5 at start of treatment			
First visit	6–9 years n=91	10–13 years n=98	14–16 years n=82
Lost during year 1	4%	14%	34%
Lost during year 2	20%	19%	29%
Lost during year 3	10%	19%	18%
Total lost to follow-up	34%	53%	82%

Treatment duration appears – quite naturally – to be associated with the degree of dropouts with lower rates in short-term treatment studies[106, 120]. The effect of SES on dropping out appears to be complex. Higher dropout rates have been reported in both lower and higher SES strata[77, 123]. In our work there were no effects observed associated with socioeconomic status. Interesting issues has been broth up by Zeller et al. They found that the lost to follow patients were more likely to live with one parent, the children reported higher degree of depressive symptoms and lower self esteem[77]. In the present study these parameters were not studied. Braet et al reported that the parents of the completers reported significant higher score of motivation but there were no differences between the children[111]. Zeller et al and Holm et al found, in the same way as in the present thesis (paper I) that the age at start of treatment to be the most influential dependent factor for not dropping out[77, 124].

It is possible that the risk for dropping out of treatment depends on a combination of reasons as above but practical external reasons may be of importance, such as lack of time travel distance and environmental conditions at the clinic, i.e., whether the ward is adapted for obese subjects. In addition, fatalistic feelings -"after all this time, I must be an impossible case" – may also contribute to increased drop out risk.

Except for age at start of treatment, we were not able to define any high-risk subgroups;

- Dropping out patients were not the heaviest or the lightest individuals
- Dropping out patients were not patients with the best or the worst results
- The results showed a trend towards higher risk among children with normal weight parents
- The risk to be lost to follow-up didn't differ between socioeconomic status in the families

The lost of follow up patients seems to be an important area for future research.

6.1.3 What is an acceptable treatment outcome?

It is important to determine and discuss the goal of treatment. As mentioned above the obvious goal should be a reduction of weight excess which results in an iso BMI< 30. However this is difficult to achieve and this outcome parameter is rarely used when obesity treatment is evaluated. The opposite position is more common, i.e., a statistically significant effect is considered as a positive treatment result independently whether the weight loss is so small that the clinical effect probably is absent[106]. Sometimes also the absence of weight gain or increase in BMI SDS is defined as a positive result[89]. In the literature it is rarely discussed what a reasonable goal is in the treatment of childhood obesity. Often the quality of life is raised as a central part. Of course, it is of importance, but for diseases associated with a reduced life expectancy, it can be questioned whether it is an acceptable primary goal. It is remarkable that several books about childhood obesity[32, 125-127], including titles such as '*Management of Childhood Obesity'* and '*Handbook of Childhood and Adolescent Obesity'* never discuss the question of acceptable treatment outcome. In my opinion, obesity is the disease we aim to treat. In order for the child to become healthier and to decrease the risk for future comorbidities, the excess weight must be reduced.

In moderately obese, prepubertal children, a halt of further weight gain in combination with normal growth in height may be regarded as a sufficient treatment. For most of the obese children this is not an option.

For the severely obese adolescent patient, behavioural treatment needs to be seen as a "palliative" and not a healing operation. The patients will be given the tools to handle and control rather than solve the problem[61]. This means that we need to explain for the patients that they should not expect to go down to normal weight and stay there. This is a lifelong disease in need of lifetime treat. In my opinion this is not an acceptable standpoint. We know that if we can help the child to reduce energy intake a normalisation of the weight will occur. On the other hand, we have to accept that behavioural treatment as we know it today is insufficient to help adolescents with severe obesity and we need to be realistic not to induce false hope. However, the treatment and thereby the weight loss needs to reach a level associated with positive effects on health. We have in our work chosen to use a decrease of ≥ 0.5 BMI SDS as a clinically significant effect since it has been demonstrated to correlate to clinically significant decrease in negative health consequences for obese children. A reduction of this magnitude was shown to lead to improvements in cardiovascular risk, insulin sensitivity and metabolic risk[69, 70, 107, 108]. These findings have later been confirmed by Ford et al.[69], who also reported that improvements in metabolic health was observed at decrease of ≥0.25 units, but greater benefits at a decrease of at least 0.5 units.

In the treatment of adults it is more common to use waist circumferences as a measure of treatment results. However, in the adult population they have seen a strong correlation between metabolic risks at clear limits[128]. Limits for children are more different and the literature gives conflicting results[129]. It is also important to remember that it is a difficult measure to take and the practical measurement has to be handled with some finesse. For the most severely obese children, you have to have special measuring-tape that lasts around and the children do not appreciate having you around the stomach.

6.1.4 How long will the treatment last and how often should we meet the patients?

It has previously been reported that the frequency of visits is of importance for the weight reduction results[130], but no such association was observed in our study. However, this is probably due to the fact that the frequency of visits was directed by the results. In one study by Nowicka et al.[89] with children in the same BMI and age range as in our entire group, the mean BMI SDS[5] decline was 0.12 units and, in another study from the same group, of adolescents[90], BMI SDS fell 0.06 units. Their mean number of visits per year was 3.8. Thus their one-year results were approximately 50% of ours, with a corresponding 50% lower visit frequency, indicating that visit frequency may be of importance for the outcome.

Only a few earlier reports have been published examining the effect of treatment duration on outcome. This may be due to the fact that most of the studies are conducted in small groups of patients in short interventions. It is unusual in the field of medicine to use short-term programs to treat chronic diseases and it is also possible that a short-term treatment would not be the optimal way to treat childhood obesity.
Reinehr et al shows in a large German cohort, followed for two years that the institutions with best results differ from the others in order to that they have higher intensity and duration and this was significantly associated with greater decrease in BMI SDS[131].

When different types of behavioral interventions are evaluated it is common to use one year results as the outcome parameter. It is not expressed but obviously presumed that one year data predicts long-term outcome[95] . Similarly, during ordinary clinical conditions it is usual that treatment is evaluated after one year and if nothing positive has happened the treatment is terminated either by the physician or the parents/patient. Our data indicates that this presumption is incorrect. There is only a poor correlation between treatment results during the first year of continuous treatment and the effect during three years
Our study indicates that it is possible to reach clinically significant reduction in BMI SDS after three years in patients without response during year one. As stated in the article conducted by Han et al;

"Because obesity is a chronic disorder needing continuing management, long-term clinical trials are needed to show safety and efficacy of treatments, not only for a few months, but also during the crucial period of active growth and maturation".

(Han et al Lancet 2010 s. 1745[48])

I couldn't agree more

6.1.5 How do we help the obese teenagers?

The severely obese adolescents had no effect at all of three years behavioural treatment. After three year of treatment only 30% in the adolescent group remained in treatment compared with 76% in the youngest age group 6-9 years. To get the teenagers to succeed with their treatment, we must first understand how we should design treatment to make them stay in treatment. We have not been able to demonstrate good results among severely obese adolescents but if they don't stay in treatment we have no possibilities at all to help them. Braet et al saw that the degree of parental motivation affected the dropout rate[111]. Maybe this will also be an explanation for a failure of support to the children and teenagers. It is plausible that the parents have given up, that they cannot cope any longer and feel that the child will cope by itself. A previous interview study of adolescent patients at National Childhood Obesity Centre concluded that we must focus on the person and the personal requests, goals and reason for weight reduction and of great importance become sensitive of the large impact obesity has on the adolescents' lives. The authors also rose the question what it meant for the patients to be obese except for the most common being bullied they brought up; worsening parental contact, difficulties to be concentrated in school and importantly fear of disease[132]. These results rises an important stand point, the adolescents need of information and clarifying about the health risks, the medical examinations and off course the results of the examinations.

Possible actions to reduce drop-outs?

- Treat the adolescents individually.
- Take into account previous weight loss attempts, what was good and what was bad.
- Help the adolescents to identify realistic expectations and realistic goals.
- Help the adolescents to identify their biggest problem right now.
- Confidence is not obvious, there is something you as therapist deserves, and trust must be earned.
- Review the equipment at the reception, are the seats and examination couches large enough.
- Offer the adolescents evening receptions, so they do not have to leave school and they can come when there are less other younger children at the clinic.
- Create a good working relationship with the adult care for in the future possible takeover.

These actions *might* reduce the drop out although the assumption is based on common sense – not evidence based medicine. Furthermore it remains to be shown whether these actions are sufficient to create weight loss among the severely obese adolescents.

6.1.6 Motivation

A lot of research groups include only patients who already from the beginning are motivated; in some studies the degree of motivation is evaluated before the start of treatment, serving as an inclusion criterion. Results from these studies are comparable to others only to a limited degree since they do not investigate the effects of treatment in the general population of obese individuals. A major concern is how we shall handle the unmotivated patients/parents? In my opinion it is not ethically correct not to treat them, obesity is a disease with reduced life expectance and what does the motivational rate tell us about the patients' possibility to benefit good treatment results? One previous study shows that the children who were extremely well-motivated at start achieved worst results[133]. In the orlistat study, we showed that the degree of willingness/motivation to decrease weight rise when the patients see that it is possible to manage a weight reduction see Figure 14 a and 14 b. They significantly perceived losing weight to be less difficult after treatment, this despite the fact that all children reported adverse events in terms of oily loose stools. However, based on these results we suggest that we can help the patients to become motivated by showing that it is possible to lose weight, to show them that they not are impossible cases. In fact it is hard to value the difference between motivation and self-efficacy, it might not be harder than to dare to say that you want to do something about your weight even though you are aware of the risk to failure. For this reason it is devastating to initiate future treatment exclusively for the motivated patients. Motivation is a difficult concept. We use it when we judge that a patient/family doesn't comply with the behavioral therapy, i.e., the patient does not lose weight. But is it correct to claim that a patient who fails within the behavioural therapy setting but want to participate in an obesity surgery study is not "motivated"? In my opinion it is not. The feeling that it is not possible to adjust to the life style changes required for weight loss is not the same as lack of motivation.

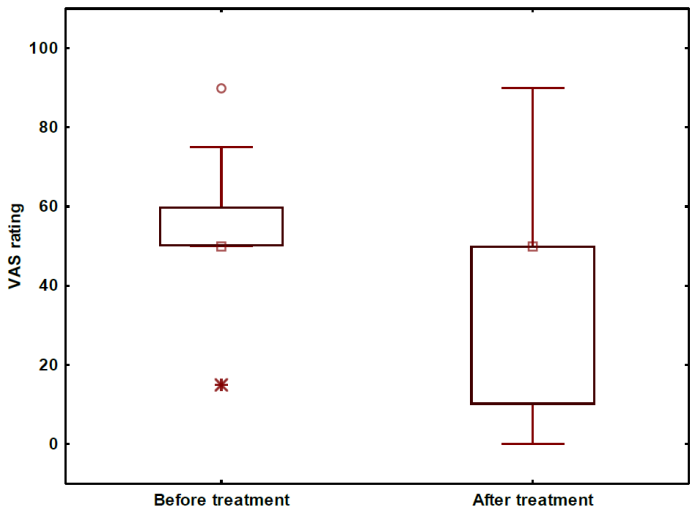

Figure 14 a. Box-plot of the children in study III about their estimation of difficulties to lose weight before and after 12 weeks orlistat treatment.

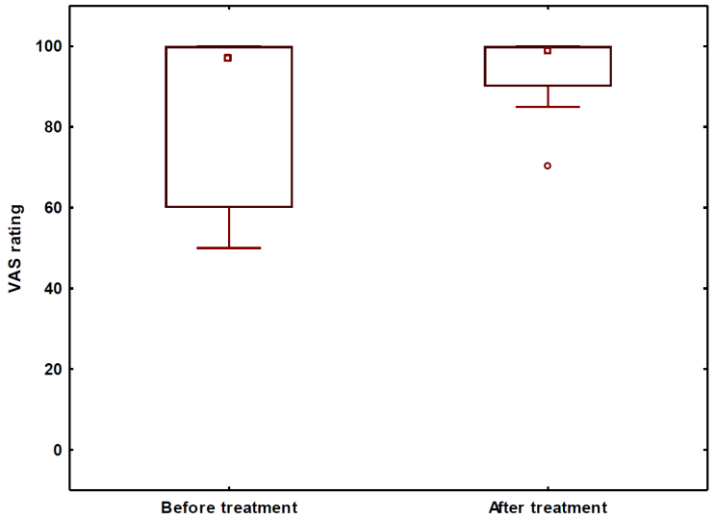

Figure 14b. Box-plot of the children in study III about their motivation to lose weight before and after 12 weeks orlistat treatment.

6.1.7 Childhood obesity and obesity drugs

I have in this thesis shown that existing drugs have a supportive effect on obesity treatment. It is especially important to help groups of children who have no other options. Table 9 shows the differences in treatment effects in this thesis expressed in kilograms, important to notice is the differences in length of treatment and to put the normal growth in perspective especially in younger age and in studies with longer duration.

Table 9. Change in kilogram for each study

	12 weeks Mean (min-max)	20 weeks Mean (min-max)	Year one Mean (min-max)	Year two Mean (min-max)	Year three Mean (min-max)
Behavioural treatment					
Completers age 6–9			7.0 (-10.6 – +34.9)	13.0 (-5.6 – +41.6)	20.0 (-10.9 – +51.9)
Completers age 10–13			5.0 (-22.6 – +50.5)	9.1 (-41.6 – +34.9)	12.6 (-33.3 – +49.9)
Completers age 14–16			1.0 (-28.3 – +43.8)	1.1 (-26.8 – +69.4)	0.6 (-44.5 – +23.8)
Orlistat treatment					
Age 7–12	-4.0 (-12.7 – +2.5)				
Sibutramine treatment					
Hypothalamic obesity age 7–20		-3.1 (-9.2 – +3.1)			
Non-hypothalamic obesity age 7–20		-5.8 (-14.3 – +6.0)			

Change in kilogram for each study. Data presented as mean and range in parenthesis.

As mentioned above the results of behavioural treatment is not sufficient for all children and for severely obese adolescents the effect is minimal. The situation is frustrating for both caregivers and families when behavioural treatment fails. It is a balancing act between the caregiver and the families, where the suffering family look for the easiest and quickest way to treatment and thus often has a strong belief in drugs. But the other side of

the coin is, as mentioned above, that we cannot blame all who are convinced that life style changes are impossible as having a low motivation to lose excess overweight.

Unfortunately, independently of the side of the coin we are looking at, there are no obesity drugs approved for obese children and adolescents in Sweden. Randomised studies of the two existing drugs Xenical® and Reductil® compared with placebo are associated with weight loss in both adults and adolescents in the range of 3 to 5kg[134, 135].

In 1998-9 several patients came to the National Childhood Obesity Centre just because they thought that they would receive Xenical®-treatment from us. When they were told that the safety of the treatment of children not was evaluated, several patients and families described "rumors" of ongoing treatment by other doctors. We therefore asked the Pharmacy to provide us the figures regarding prescription of Xenical® to children and adolescents in Sweden. To our surprise, the parents were right, Xenical® was indeed prescribed for children see Table 10. This led us to plan and implement the Xenical® study.

Table 10. The number of prescriptions distributed for Xenical® to children aged 0-18 years during year 1999.

Age	Distributed packages of Xenical® 1x84 to residents of Stockholm County Councils	Distributed packages of Xenical® 1x84 to residents of Sweden
1		
2		
3		2
4		1
5		
6		
7		
8	7	7
9	5	6
10	5	11
11	10	20
12	11	15
13	0	15
14	6	32
15	8	65
16	9	102
17	45	236
18	86	5081

Initially the efficacy was overestimated. The drugs were prescribed too widely to patients who did not belong to the intended patient population, see Table 10. Xenical® should be seen as an adjunct to concomitant lifestyle change programs. We do not currently use Xenical® but for children who understand the relationship between fat intake and risk for oily stools Xenical® should be possible to use to induce behavioural changes which are supported by our present results.

In this thesis I have shown that sibutramine treatment is effective also for children with hypothalamic obesity and for obese children with aggravating problems that makes life style changes extremely difficult to achieve. The planning of the Sibutramine Study started when we treated a 16 year old girl with the drug under license. This girl had undergone surgery for craniopharyngioma, where after she developed a morbid obesity, weight 186 kg and 150 cm, BMI 83. Her weight decreased 73 kg after 6 months of treatment. Weight loss was certainly to a great extent a loss of body fluid but changed her possibility to make other lifestyle changes drastically. This is a type of patient with extreme morbid obesity that we cannot help without pharmacological treatment. Obesity surgery would be considered too dangerous.

6.1.8 Blood pressure

Many studies in adults involving the drug sibutramine have shown a slight blood pressure and heart rate increase[136]. We could not report any of this in our study. The simplest explanation for this is of course that our patients have young vessels, yet unaffected by vessel inflammative processes. The patients in the sibutramine study are not among the most cooperative and it is difficult to get them to lie still. Thus another possibility is that the results therefore are not as accurate as those obtained in adults. However it is unlikely that marked variations in blood pressure should have been unnoticed.

In January 2010 the European Medicines Agency (EMEA) decided to remove Reductil® from all markets in European Union due to that the risks of the medicine are greater than their benefits among middle age obese subjects. The basis for this was the SCOUT study[137], a study conducted by Abbott laboratories to investigate how the drug acts in patients with cardiovascular risk factors which in itself is confusing when sibutramine was contra-indicated with cardiovascular disease[138].

It is questionable, whether the decision to remove the only antiobesity drug with documented effects for children and adolescents with hypothalamic obesity can be justified based on one study in a middle aged adult population with high cardiovascular risk.

6.2 METHODOLOGICAL CONSIDERATIONS

6.2.1 Control groups

Randomized controlled studies (RCT) are the only studies with a high value in the world of evidence based medicine. This is so fundamental that it is difficult to publish clinical data if there are no control groups. Although, this makes sense at the first sight but it may cause problems when chronic diseases are studied. Is a short-term RCT of higher value compared with a long-term uncontrolled follow-up? I have in this thesis shown that there is a very poor correlation between one year treatment results compared with three years. Therefore one year RCT results within the field of childhood obesity may be of minor clinical value. On the other hand untreated control groups are unethical in long-term studies. Which children should go for years without treatment? Nowicka et al used a control group from a waiting list, but found that they during the study period decreased

their weight[139]. It is possible that the waiting list controls in their minds already have started their treatment, their problem has been confirmed therefore they cannot be compared with an untreated group. In paper I we instead used children participating in the obesity prevention study STOPP[112]. This was performed to be able to contrast behavioural treatment for the youngest age group from spontaneous changes. This could be done since no intervention effect was reported among the obese children. Today the ethical committee considers it unethical to delay treatment for four year old children during two years (personal communication Nowicka P, application number 2011/1329-31/4). Thus we either have to reconsider the evidence value of uncontrolled studies or rely upon short-term RCTs with low clinical value.

6.2.2 Wash out period

In most placebo-controlled crossover drug studies have a wash-out period placed between the placebo and active substance period. We chose not to have it in paper IV. This decision was made on two assumptions; first, we do not believe that the placebo effect will affect these children due to underlying sickness and mental handicap. Second, we also wanted to make the study time so short and efficient as possible as these patients, because of their underlying illness, spend and has spent a lot of time in hospital.

6.3 STATISTICAL CONSIDERATION

6.3.1 Various classifications of degree of obesity

BMI SDS is a method for comparisons of BMI values with a reference population to be able to compare children of various ages and genders. It can be difficult to compare studies conducted in different research groups and above all from different countries when they use different reference populations to calculate the degree of obesity in form of BMI SDS. For example, in this thesis two different reference groups, differing significantly, were used. The difference depends mainly on the fact that they were collected at different times, i.e. before and after the obesity epidemic. This led us to the conclusion that the latter[5] is more permissive for the same individual. The significance of this phenomenon is not crucial as long as we compare the same individuals over time. But the readers need to be aware of the differences.

6.3.2 How to handle missing data and patients lost to follow up?

There are several different methods to use for handling patients lost follow in a correct way. We have used two different intention to treat analyses based on following thoughts; last observation carried forward method (LOCF) is normally regarded as a conservative method for replacing missing data, in obese children this method may underestimate the levels of BMI SDS since they may increase over time. Therefore, we in paper I and II we also used baseline value carried forward method (BVCF) as an even more conservative method for replacing missing data. Interestingly, regardless of the method used to handle missing data, the same trend was observed see Figure 15 a-c.

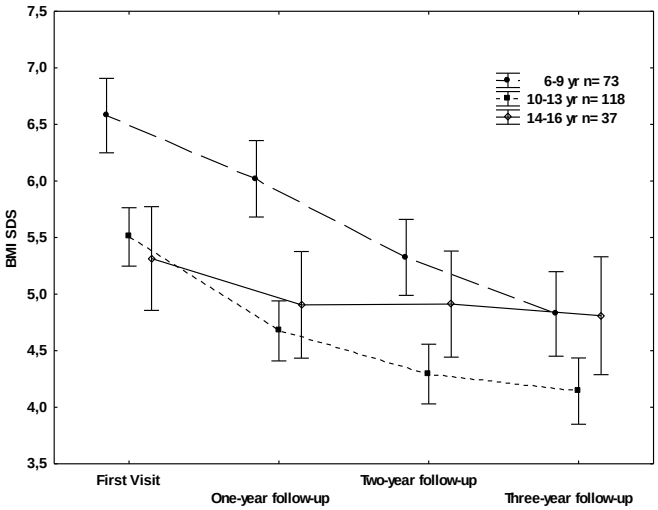

Figure 15a**.** Completers population

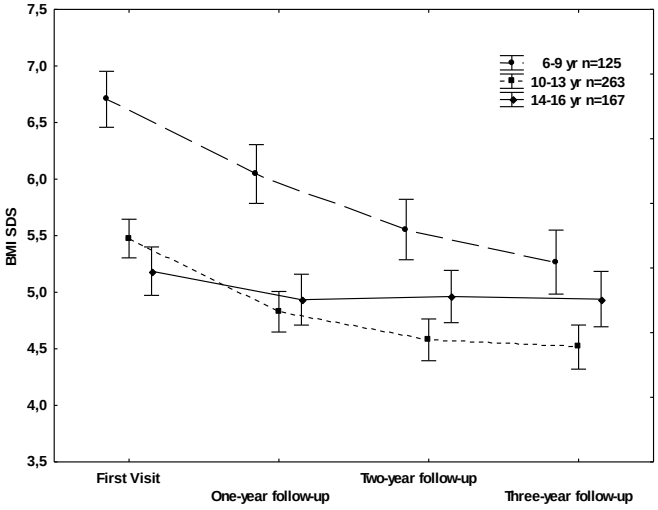

Figure 15b. Last Observation Carried Forward method (LOCF).

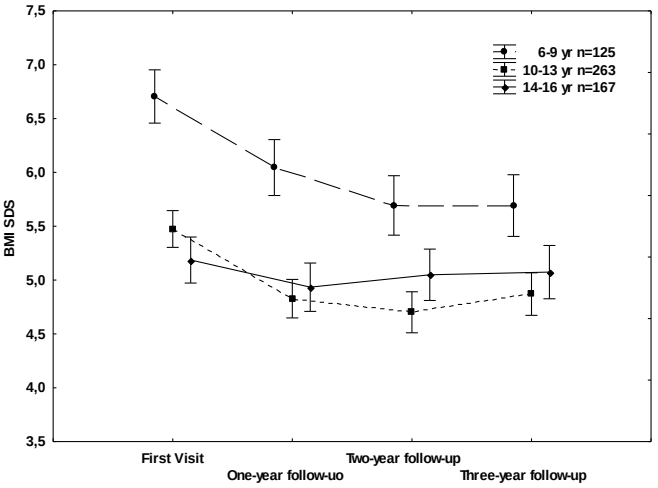

Figure 15c. Baseline Value Carried Forward method (BVCF).

6.4 STRENGTHS AND LIMITATIONS

The orlistat study is still the only one conducted and published in prepubertal children and the sibutramine study the only one examining the treatment in these groups of children with special needs.

The works with behavioural treatment is strengthened by the large sample size and long treatment duration. The last Cochrane review[95] identified 54 trials of behavioural interventions. In these trails the sample size was 16 to 218 participants and 70% of the studies included fewer than 30 children. The study period was below 6 months in 26 %, 6-12 months in 67 %. No studies had a longer treatment period than two years (n=54)[95] .

A major limitation is the lack of untreated randomised age matched control groups. As discussed above we found it unethical to have untreated control groups in long-term studies. A waiting-list procedure would have posed the same problems. In addition, our observations regarding the poor correlation between the results of one year of treatment and three years of continuous treatment, the association between lost of follow-up rate and age at start of treatment and finally the lack of correlation between SES and outcome are all independent of control groups.

Another limitation is that the material lack data of ethnicity, family relations, distance and route to the clinic. It must also be kept in mind that this is a selected material with severely obese subjects, and that all participants are referred to the National Childhood Obesity Centre. Thus, it is possible that the outcome of behavioural treatment had been better in other clinical settings. However, to the best of my knowledge no studies have presented good outcome of life style interventions for severely obese adolescents.

6.5 CONCLUSIONS AND CLINICAL RECOMMENDATIONS

- It is possible to successfully treat children with behavioural modification, if it is initiated at an early age, preferably between 6-9 years of age. In this age group the results were very good also for those with severe obesity.

- None of the specific factors, heredity, socioeconomic status and age at onset of obesity affected the effect of treatment in any age group.

- One year results poorly predict the three year outcome. It should be clearly stated for the families that independently of the results of treatment the children and adolescents should remain in treatment for several years.

- Far too many children and adolescents drop out from treatment prematurely; the major reason to be lost to follow-up was patient/parents decision to stop treatment. Age is an important predictor for patients being lost to follow-up, only 30% of the adolescents remained in treatment for three years. However we were not able to identify other factors of importance for drop out and this is an important area for future research.

- Severely obese adolescents had no effect at all of behavioural treatment. The poor treatment effect in combination with high dropout rates are major challenges in adolescent obesity treatment. Severe obesity in adolescents is associated with poor outcome both from a psychosocial point of view and from a health perspective. Thus this is the group in the greatest need of treatment and it is urgent to develop new treatments for them

- The children were able to comply with the Xenical® treatment and adapt food intake to reduce side effects. This resulted in weight loss. However, all children reported orange, oily stools after intake of high fat diet. The children became more interested in weight reduction and perceived losing weight to be less difficult after Xenical® treatment. Multivitamin supplementation should be added during orlistat treatment. In the treatment of childhood obesity, Xenical® can with great advantages be used as a contributing component in the process of changing behaviour.

- Sibutramine induced a significant weight reduction, for children with obesity and other aggravating syndromes and for the children with hypothalamic and syndromal obesity. Sibutramine was well tolerated and the side effects minimal. However, 94% of the patients with hypothalamic obesity and 66% of patients with non hypothalamic obesity required increased sibutramine dose (15mg). We consider Sibutramine as a possibly useful drug for children with hypothalamic obesity provided that can get the approval from Swedish Medical Products Agency.

One major finding in this thesis is that it is possible to treat severely obese children successfully if treatment is initiated early in life. However we are not there yet. The BORIS-registry indicates that we in Sweden are on the right track but still most children are not treated for obesity and if they are, they often start too late. If we can lower the age at start of treatment, we will be able to help many more to a more healthy weight with existing behavioural treatment. This is independent of degree of obesity at start of treatment, heredity, gender, age at obesity onset and socioeconomic status. Regardless if age dependent results are due to physiological mechanisms or differences in compliance, this treatment is more effective in young patients. Early intervention is important, not only for the benefit of the treatment, we also know that obesity can be persisting from as young age as seven years olds. 92% of the severely obese adolescents were already overweight and obese at age 7. Our data indicates that if they had been identified and offered treatment, it is likely that 75% of them had been able to reach a clinically significant decrease of 0.5 BMI SDS units after three year of behavioural treatment. In the future, adolescents with morbid obesity will probably earlier than before become candidates for pharmacological and/or surgical treatment to reach a healthier life and lifestyle. Although the obesity prevalence is higher among children from lower socioeconomic status groups they all have the same ability to benefit from treatment. All obese children should have same right to get help from the health care system.

Lifestyle changes can never be replaced by drugs or obesity surgery. However, it is likely that drugs and obesity surgery are important means to induce life style changes. Most probably if no remarkable developments within the field of behavioral therapy occur, both drugs and obesity surgery will be used more frequently in the future.

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